LIPID-LOWERING THERAPY

IN

CALCIFIC AORTIC STENOSIS

BY

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ABSTRACT

Background Calcific aortic stenosis is the commonest valvular heart condition seen in the western world and appears to be the result of an active inflammatory process closely resembling atherosclerosis. I hypothesised that (a) risk factors for atherosclerosis would predict, and (b) lipid-lowering therapy would retard, disease progression and clinical outcome in patients with calcific aortic stenosis.

Objectives (i) To compare the magnitude and reproducibility of measures of valvular stenosis and calcification, (ii) to determine the effect of intensive lipid-lowering therapy on disease progression and clinical outcome, and (iii) to describe predictors of disease progression and clinical outcome in patients with aortic stenosis.

Methods These issues were addressed in the context of a randomised controlled trial of which I was study co-ordinator. In the Scottish Aortic stenosis and Lipid-lowering Therapy, Impact on REgression (SALTIRE) trial, 155 patients aged 68 ± 11 years (range 34-85) with aortic valve stenosis were randomised, and underwent helical computed tomography (CT) and Doppler echocardiography. Seventy-seven patients were assigned to atorvastatin 80 mg daily and 78 to matched placebo over a median period of 25 months. Of the 155 patients, 102 had detectable coronary artery calcification on CT with 48 of these patients being randomised to atorvastatin and 54 to placebo.

Results (i) *Stenosis severity*: Doppler echocardiography demonstrated a mean aortic jet velocity of 3.45 ± 0.66 metres per second (m/s) and a peak gradient of 49 ± 11 millimetres of mercury (mmHg). Computed tomography and Doppler echocardiography showed good reproducibility. The median aortic valve calcium (AVC) score was 5858 Hounsfield units (HU) (interquartile range, 1555-14596) and this positively correlated with aortic jet velocity and peak gradient ($r=0.54$, $p<0.0001$ for both). (ii) *Disease progression*: Aortic jet velocity increased by 0.199 ± 0.210 m/s per year in the atorvastatin group and 0.203 ± 0.208 m/s per year in the placebo group ($p=0.95$; adjusted mean difference, 0.002; 95% confidence interval (CI)), (-0.066 to +0.070 m/s/yr). Progression in valvular calcification was 22 ± 21% per year in the atorvastatin group, and 22 ± 20% per year in the placebo group ($p=0.93$; ratio of post-treatment AVC score, 0.998; 95% CI, 0.947 to 1.050). The rate of change in coronary artery calcification was 26% per year (0.234 ± 0.037 log arbitrary units/yr (LogAU/yr); $n=39$) in the atorvastatin group and 18% per year (0.167 ± 0.034 LogAU/yr; $n=49$) in the placebo group: geometric mean difference of +7% per year (95% CI, -3% to +18%; $p=0.18$). (iii) *Lipid-lowering*: Atorvastatin reduced serum low-density lipoprotein (LDL) cholesterol (-53%; $p<0.001$) and C-reactive protein (CRP) (-49%; $p<0.001$) concentrations whilst there was no change with placebo (-7% and +17%; $p>0.95$ for both). There was no correlation between serum LDL concentrations and the progression of aortic stenosis or coronary calcification. (vi) *Predictors of disease progression and outcome*: Aortic valve disease progression was predicted by age, sex, height, hypertension, serum brain natriuretic peptide (BNP) concentration, and baseline valve disease severity. Clinical outcome was predicted by baseline and rate of progression of aortic stenosis severity and serum

BNP concentrations.

Conclusions Calcification of the aortic valve is closely associated with the severity of aortic stenosis with heavy calcification suggesting the presence of severe aortic stenosis that requires urgent cardiological assessment. In contrast to observational studies, intensive lipid-lowering therapy does not halt the progression or induce regression of aortic stenosis or coronary artery calcification. However, our studies cannot exclude a small reduction in disease progression or a significant reduction in major clinical end-points. Long-term, large scale, randomised, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis. The major predictors of disease progression and clinical outcome remain baseline measures of disease severity; namely aortic jet velocity, aortic valve calcification and serum BNP concentration. With the exception of hypertension, the presence of atherosclerotic risk factors and vascular disease are not predictive. Our findings suggest that atherogenesis does not provide a major contribution to the progression of aortic stenosis.

To Megan and Callum

CONTENTS

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ANOVA	Analysis of variance
AS	Aortic stenosis
AU	Arbitrary units
AVA	Aortic valve area
AVC	Aortic valve calcium
AVR	Aortic valve replacement
BNP	Brain natriuretic peptide
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
CVA	Cerebrovascular accident
HDL	High-density lipoprotein
HMG CoA	Hydroxymethylglutaryl coenzyme A
HsCRP	Highly sensitive C-reactive protein
HU	Hounsfield units
ICAM-1	Intercellular adhesion molecule-1
ITT	Intention-to-treat
LAD	Left anterior descending
LDL	Low-density lipoprotein
Lp (a)	Lipoprotein a

LVOTD	Left ventricular outflow tract diameter
MR	Magnetic resonance
NYHA	New York Heart Association
PLSD	Protected least squares difference
PWA	Pulse wave analysis
SALTIRE	The **S**cottish **A**ortic stenosis and **L**ipid lowering **T**herapy **I**mpact on **RE**gression trial
SD	Standard deviation
SE	Standard error
VCAM-1	Vascular cell adhesion molecule-1

DECLARATION

This thesis represents research undertaken in the Department of Cardiology at the Royal Infirmary and Western General Hospital in Edinburgh. The substantial part of the work described has been my own and carried out during the period between 2000 and 2004 whilst I was a Clinical Research Fellow. As the SALTIRE trial study co-ordinator I was involved in all aspects of the study including ethics submissions, recruitment and randomisation, data collation and analysis, and writing for publication. I have received help and advice from many colleagues, and they have been formally acknowledged. The thesis has not been accepted in any previous applications for a degree and all sources of information have been acknowledged. The work has been published in peer-reviewed journals: see Bibliography.

Sarah Joanna Cowell 31st March 2007

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CHAPTER 1

CALCIFIC AORTIC STENOSIS

Based on

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1.1 INTRODUCTION

Aortic stenosis is the commonest adult heart valve condition seen in the western world. It may be the result of a congenital lesion, or it can arise following rheumatic fever. More commonly it occurs as a result of calcification of a congenitally bicuspid or a trileaflet aortic valve (calcific aortic stenosis). Over the last 30-50 years, its diagnosis and management has been revolutionised by the development of invasive (cardiac catheterisation) and non-invasive (echocardiography) haemodynamic assessments as well as potentially curative cardiac surgery. Recent insights have been made into the pathogenesis of calcific aortic stenosis, resulting in speculation that the disease mimics atherosclerosis and progression could be delayed or prevented by the use of lipid-lowering therapy. If confirmed, such pharmacological therapy may have the potential to reduce the need for aortic valve surgery.

1.2 EPIDEMIOLOGY

Calcific aortic stenosis was first documented in 1904 [Monckeburg 1904] and at that time was regarded as uncommon. In the 19th century, calcific aortic stenosis was not recognised as a clinical entity since pathological studies revealed only cusp thickening and sclerosis [Osler 1886]. As a result, aortic valve sclerosis (thickening without stenosis) and aortic valve stenosis were regarded as different pathological conditions for many decades. Recent evidence, however, suggests that they represent different stages of the same disease process [Stewart *et al* 1997; Cosmi *et al* 2002; Faggiano *et al* 2003]: sclerosis arising from the development of valvular calcific

lesions that progress slowly over several decades before ultimately causing aortic stenosis [Mensah and Friesinger 1996]. The current prominence of calcific aortic valve disease is likely to represent increased human longevity together with the decline in rheumatic valvular heart disease.

Aortic valve sclerosis is present in 20-30% of individuals over 65 years and 48% over 85 years [Otto *et al* 1999], and aortic stenosis in 2% and 4% respectively [Lindroos *et al* 1993; Stewart *et al* 1997; Otto *et al* 1999]. Calcific sclerosis and valvular stenosis occur in patients with both a normal tricuspid aortic valve as well as in those with a bicuspid valve. The prevalence of bicuspid aortic valves is difficult to determine but is estimated to affect 1-2% of the general population [Ward 2000]. Up to 70% of patients with a bicuspid aortic valve develop valvular stenosis [Ward 2000] and will typically require aortic valve replacement (AVR) one to two decades earlier in life (fifth to sixth decade) than in those with a tricuspid aortic valve.

1.3 NATURAL HISTORY

Prior to the introduction of haemodynamic assessment and cardiac surgery, the natural history of aortic stenosis was described by its clinical presentation. Calcific aortic stenosis is a gradually progressive disease, characterised by a long asymptomatic phase lasting several decades, followed by a shorter symptomatic phase usually associated with severe narrowing of the aortic valve orifice.

The outlook for patients with asymptomatic aortic stenosis is generally good and closely matches that of life table estimates for age and sex matched controls

[Pellikka *et al* 1990]. A striking feature of aortic stenosis is that the prognosis changes dramatically with the onset of symptoms in association with severe outflow obstruction: a 2-year survival rate of 50%. Although few studies specifically assessed the influence of age, patients over the age of seventy have a worse prognosis with 2- and 3-year survival rates of 37% and 25% respectively [O'Keefe *et al* 1987]. The prognosis also depends upon the clinical presentation with a mean survival of 3 years for those presenting with angina and syncope, 2 years with the onset of breathlessness, and as little as 1 year in those who develop overt left ventricular failure [Ross and Braunwald 1968; Aronow *et al* 1993].

1.3.1 OTHER CARDIOVASCULAR EVENTS

Despite the favourable outlook in those patients with mild asymptomatic disease, there is an increased risk of cardiovascular events unrelated to the aortic valve disease. Otto and colleagues demonstrated that, in patients with aortic sclerosis, there is a 50% increased risk of myocardial infarction and cardiovascular death even in the absence of significant outflow tract obstruction [Otto *et* al 1999]. The Helsinki Ageing Study also suggested that patients with moderate to severe aortic stenosis had higher all cause and cardiovascular mortality irrespective of associated symptoms. In particular, a higher rate of stroke related death was noted although the majority of these patients had atrial fibrillation [Iivanainen *et al* 1996].

1.4 PATHOLOGY OF CALCIFIC AORTIC STENOSIS

For many decades, calcific aortic stenosis has been attributed to prolonged "wear and tear" and age-associated valvular degeneration. Contrary to this supposition, however, is the absence of aortic valve calcification or stenosis on echocardiography in a third of individuals over the age of 80 [Lindroos *et al* 1993]. Recent evidence suggests that calcific aortic stenosis may result from an active inflammatory process involving biochemical, humoral and genetic factors.

1.4.1 HISTOLOGY

Normal aortic valve leaflets are macroscopically smooth, thin and opalescent, with clearly defined tissue layers at a microscopic level and very few cells [Olssson *et al* 1994]. Increasing age gives rise to non-specific thickening of the tips of the valve leaflets, with an increase in the number of adipose cells and thinning of tissue layers [Otto *et* al 1994]. In calcific aortic stenosis, there is characteristic leaflet thickening, with irregular nodular masses on the aortic aspect of the valve. Microscopic assessment of both mild and severely affected valves reveals endothelial and basement membrane disruption, with underlying subendothelial thickening. The lesion itself contains disorganised collagen fibres, chronic inflammatory cells, lipoproteins, lipid, extracellular bone matrix proteins and bone mineral [Olsson *et al* 1994; Otto *et al* 1994].

1.4.2 PATHOGENESIS

The histological features described closely resemble those seen in atherosclerosis and are strongly suggestive of chronic inflammation. In calcific aortic stenosis, the factors initiating the inflammatory process have not been identified but mechanical injury to the endothelium is thought to pave the way for subsequent inflammation. This concept is supported by the pattern of aortic valve cusp involvement that corresponds to areas of low shear and high tensile stress: namely the aortic surface of the leaflets and predilection for the non-coronary cusp [Thubrikar *et al* 1986; Cujec and Pollick 1988; Yearwood *et al* 1989; Otto 2002]. Congenitally bicuspid aortic valves are less efficient than tricuspid valves at distributing mechanical stress and this may account for their predilection to develop rapidly progressive stenosis [Beppu *et al* 1993].

1.4.2.1 *Role of lipids*

Endothelial injury or disruption may allow circulating lipids to enter the valvular interstitial tissue [O'Brien *et al* 1996] and accumulate in areas of calcification and inflammation [O'Brien *et al* 1996; Olsson *et al* 1999]. The lipoproteins implicated in atherogenesis, including low-density lipoprotein (LDL) and lipoprotein (a) (Lp (a)), are present in early aortic valve lesions [O'Brien *et al* 1996] and undergo oxidative modification [Olsson *et al* 1999]. These oxidised lipoproteins are highly cytotoxic [Chisholm 1991] and capable of stimulating inflammatory activity [Berliner *et al* 1990; Rajavashisth *et al* 1990] and mineralisation [Hirsch *et al* 1993; Sarig *et al* 1994; Parhami *et al* 1997].

1.4.2.2 *Inflammation*

Both macrophages and activated T lymphocytes are present in the early and advanced lesions of congenitally bicuspid [Wallby *et al* 2002] and tricuspid aortic valves [Olsson *et al* 1994; Otto *et al* 1994]. Migration of these effector inflammatory cells appears to be mediated through increased endothelial expression of cellular adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) [Ghaisas *et al* 2000; Müller *et al* 2000]. Once recruited into the subendothelium, the inflammatory cells release enzymes, such as matrix metalloproteinases, that cause degradation of collagen, elastin and proteoglycans within the aortic valve cusps [Edep *et al* 2000].

1.4.2.3 *Calcification*

Mineralisation is a characteristic of both atherosclerotic and aortic valve lesions, and arises in close proximity to areas of inflammation. It is a prominent feature in calcific aortic stenosis and has been demonstrated in early [Otto *et* al 1994] as well as advanced lesions [Mohler *et* al 2001]. Surgically excised valves have even revealed areas of mature lamellar bone, haemopoietic marrow and bone remodelling [Mohler *et al* 2001]. Several features suggest the presence of an active highly regulated process closely resembling developmental bone formation [Boström *et al* 1995; Demer 1995].

The initiation of mineralisation (nucleation) may be stimulated by the presence of cellular degradation products following apoptosis [Kockx and Herman 1998] or by the presence of oxidised lipids [Olsson *et al* 1999; Mohler *et al* 2001]. *In vitro*

studies of cultured explants of stenotic valves have identified cells with osteoblastic characteristics capable of phenotypic differentiation and spontaneous calcification [Mohler *et al* 1999]. Their origin is unknown but they may be derived from a pool of circulating immature pluripotent mesenchymal cells [Prockop 1997]. These osteogenic cells or "calcifying valvular cells" express and produce a variety of regulatory bone matrix proteins including osteopontin [O'Brien *et al* 1995; Mohler *et al* 1997] and bone morphogenetic protein [Mohler *et al* 2001].

1.4.3 Similarities and differences with atherosclerosis

Although the similarities with atherosclerosis were recognised as long ago as 1917 [Libman 1917], they were largely disregarded until recently [Roberts 1986; Mohler 2000; Demer 2001]. The histological studies described above have highlighted the common features but also confirmed differences in the cellular and mineral components of the two lesions.

Smooth muscle proliferation and lipid-laden macrophages (or foam cells) are prominent features of vascular atheroma but are virtually absent in stenotic aortic valves. In addition, mineralisation is an earlier and more extensive feature of aortic valve lesions compared with atherosclerosis [Otto *et al* 1994]. These differences may, in part, explain why only 40% of patients with severe aortic stenosis have significant coronary artery disease [Lombard and Selzer 1987; Vandeplas *et al* 1988; Mautner and Roberts 1992; Rapp *et al* 2001; Peltier *et al* 2003] and why the majority of patients with coronary artery disease do not have aortic stenosis. As the underlying pathology for the two conditions appears to be similar, it is likely that

other unknown factors influence the development of valvular as opposed to vascular lesions [Otto and O'Brien 2001].

1.5 CLINICAL PRESENTATION

Patients present with either an incidentally noted asymptomatic systolic murmur or with symptoms of severe disease including angina, exertional syncope, breathlessness, and reduced exercise tolerance or lethargy. In simple terms, progressive obstruction to outflow results in a gradual rise in left ventricular pressures, left ventricular hypertrophy, and diastolic dysfunction. Once the degree of stenosis is severe, further small decreases in aortic valve area (AVA) result in large changes in the pressure gradient across the valve. Symptoms and decompensation arise due to the development of inadequate cardiac reserve, myocardial oxygen demand mismatch or pressure overload of the left ventricle. Symptoms rarely occur unless the degree of stenosis is of at least moderate severity (with an AVA of less than 1.0 cm^2) but patients may remain asymptomatic for long periods with even very severe stenosis [Lombard and Selzer 1987].

1.5.1 CLINICAL RISK FACTORS

In keeping with the apparent parallels with atherosclerosis, calcific aortic stenosis is associated with coronary artery disease [Mautner and Roberts 1992; Peltier *et al* 2003] and many of its risk factors (Table 1.1) [Stewart *et al* 1997]. Calcific aortic stenosis is also seen in association with severe homozygous familial hypercholesterolaemia, and its development appears to be influenced by the length of

exposure to elevated serum cholesterol concentrations [Rallidis *et al* 1998]. Interestingly, aggressive lipid-lowering therapy with plasmapheresis has been reported to regress aortic stenosis in such patients [Keller *et al* 1986]. Milder forms of hypercholesterolaemia have also been associated with calcific aortic stenosis [Aronow *et al* 1987; Wilmshurst *et al* 1997; Chui *et al* 1999], particularly in patients with non-rheumatic tricuspid valves [Chui *et al* 1999].

TABLE 1.1 Risk factors for calcific aortic stenosis

Clinical	Biochemical
Age	Hyperlipidaemia (LDL and Lp (a))
Male sex	Hypercalcaemia
Smoking	Elevated serum creatinine
Hypertension	
Diabetes mellitus	
Coronary artery disease	
Chronic renal failure	
Paget's disease	
Hyperparathyroidism	

LDL - Low-density lipoprotein; Lp (a) - Lipoprotein a.

Conditions affecting calcium metabolism, such as chronic renal impairment with secondary hyperparathyroidsim [Maher *et al* 1987; Straumann *et al* 1992; Umana *et al* 2003] and advanced Paget's disease [Hultgren 1998], predispose individuals to aortic valve calcification and accelerated stenosis. Such patients also tend to have

diffuse cardiac calcification affecting the mitral valve, myocardium and conducting system.

A number of twin studies and case reports suggest that hereditary factors may influence the development of calcific aortic valve stenosis [Lewis and Henderson 1990; Tentolouris *et al* 1993]. There has been a single report of a genetic association between aortic stenosis and a vitamin D receptor polymorphism [Ortlepp *et al* 2001] but this finding has yet to be confirmed.

1.6 INVESTIGATIONS

The assessment of valvular stenosis and monitoring of disease progression has only been possible over the last five decades using cardiac catheterisation, echocardiography and more recently magnetic resonance (MR) imaging and computed tomography (CT). Magnetic resonance may have some advantages over echocardiography in assessment of stenosis severity [Didier *et al* 2000], but its availability is limited and measurements are time consuming to perform. Although currently limited to clinical research, electron beam CT has recently been validated as a means of quantifying aortic valve calcification [MacMillan *et al* 1988; Lippert *et al* 1995; Kizer *et al* 2001]. However, echocardiography remains the current gold standard for monitoring of disease progression and left ventricular function in patients with aortic stenosis.

The severity of aortic valve stenosis is assessed using both two-dimensional and Doppler echocardiography (Table 1.2). Narrowing of the aortic valve orifice results in acceleration of blood flow across the valve. Using spectral Doppler, the velocity of blood passing through the left ventricular outflow tract (pre-valve) and aortic valve orifice (post-valve) can be measured and is usually expressed in metres per second (m/s). The peak instantaneous pressure gradient across the aortic valve has a simple relationship with the peak post-valve velocity and is described as four times the square of the velocity (modified Bernoulli equation). For example, a peak post-valve velocity of 4 m/s gives an instantaneous pressure gradient of $4 \times 4^2 = 64$ millimetres of mercury (mmHg). Where there are concerns that impaired left ventricular function limits the ability to generate an adequate pressure gradient across the valve, measurement of the AVA may need to be made using direct planimetry or indirectly using the continuity equation. On occasions, dobutamine stress echocardiography may be used as a method of distinguishing true aortic stenosis causing left ventricular dysfunction from aortic pseudostenosis where the impairment of the left ventricle causes poor excursion of the aortic valve cusps giving the impression of stenotic valvular restriction.

TABLE 1.2 Echocardiographic measures of severity of aortic stenosis

	Normal	Mild AS	Moderate AS	Severe AS
Peak post valve velocity (m/s)	0.9-1.8	2.5-3.0	3.0-4.0	> 4.0
Peak gradient (mmHg)	< 25	25-36	36-64	> 64
Aortic valve area (cm^2)	2.0 - 3.5	1.0-2.0	0.5-1.0	< 0.5

AS - aortic stenosis.

1.6.1 DISEASE PROGRESSION

Echocardiography provides the most accurate evaluation of disease progression, which can be unpredictable and extremely variable. Some individuals show little or no evidence of deterioration over time, yet others progress rapidly from mild to severe stenosis within a few years.

In patients with aortic valve sclerosis, progression to stenosis (arbitrarily defined as a peak post-valve velocity ≥2.5 m/s, or peak gradient ≥25 mmHg) is a relatively slow process with mean increases in peak post-valve velocity and peak gradient of 0.07 m/s and 1.4 mmHg per year respectively [Faggiano *et al* 2003]. However, once the valve is classified as stenotic, disease progression is more rapid with average increases of 0.3 m/s and 7-8 mmHg per year, corresponding to a decrease in AVA of 0.1 cm^2 per year [Roger *et al* 1990; Faggiano *et al* 1992; Peter *et al* 1993; Brener *et al* 1995; Otto *et al* 1997].

1.6.2 PREDICTORS OF DISEASE PROGRESSION AND CLINICAL OUTCOME

Disease progression and clinical outcome have been linked to many of the risk factors for calcific aortic stenosis including age, male sex, hyperlipidaemia, hypertension, diabetes mellitus, smoking, hypercalcaemia and chronic renal impairment [Peter *et al* 1993; Bahler *et al* 1999; Palta *et al* 2000; Ngo *et al* 2001; Wongpraparut *et al* 2002]. However, much of the evidence is conflicting and limited by the retrospective nature of the studies. The most consistent and strongest predictors of disease progression are severity of stenosis at baseline [Otto *et al* 1997; Bahler *et al* 1999] and degree of valvular calcification [Davies *et al* 1991;

Bahler *et al* 1999]. The more severe the stenosis at baseline and the more heavily calcified the valve, the faster the rate of progression. Clinical outcome is also influenced by the degree of valvular calcification, with nearly 80% of patients with moderate to severe calcification who progress rapidly (>0.3 m/s/yr) either dying or undergoing AVR within 2 years [Rosenhek *et al* 2000].

1.7 MANAGEMENT OF CALCIFIC AORTIC STENOSIS

At the present time, there is no known therapy that can slow or reverse disease progression in patients with calcific aortic stenosis. Current management includes monitoring disease progression, and ensuring patient awareness of the need for antibiotic prophylaxis against infective endocarditis. For those patients with severe symptomatic disease, the therapeutic options include conventional medical therapy for symptom control and AVR.

1.7.1 GENERAL ADVICE

All patients should be advised of the need for antibiotic prophylaxis against endocarditis for dental and other invasive procedures. Patients with moderate or severe disease should be advised to avoid strenuous physical exercise and competitive sport because of the risk of sudden death, and to report promptly the onset of symptoms.

1.7.2 MONITORING OF DISEASE PROGRESSION

Since disease progression is so unpredictable, the majority of patients should be reviewed regularly to monitor changes in stenosis severity and watch for the onset of symptoms. As a rule of thumb, asymptomatic patients with mild to moderate stenosis require review and echocardiography every 1-2 years, and those with moderate to severe stenosis every 6-12 months. Patients developing symptoms between appointments should be reviewed immediately.

1.7.3 ASYMPTOMATIC SEVERE AORTIC STENOSIS

One contentious area of management is determining the optimal timing for AVR. It is universally accepted that surgery is indicated as soon as symptoms appear in patients with severe stenosis. Although many cardiologists are loath to refer patients without symptoms for valve surgery, there are some who feel uncomfortable managing patients with severe asymptomatic valvular stenosis because of the potential risk for sudden cardiac death. However, this is rare and occurs in less than 1% of asymptomatic patients per year [Bonow *et al* 1998]. The combined risk of AVR (2-10% mortality) and prosthesis-related complications (2-3%/yr) is thus greater than the risk of sudden cardiac death. "Watchful waiting" is therefore recommended.

The onset of symptoms in patients with severe stenosis may be subtle and insidious, particularly in the elderly where co-morbidity may mislead or obscure the presentation. For this reason careful history taking for changes in exercise tolerance

as well as the classical symptoms of breathlessness, chest pain and syncope is required. In cases where patients may be underplaying symptoms, attributing them to "old age", or unknowingly avoiding activity that induces symptoms, physician supervised exercise testing may be helpful in both revealing symptoms as well as determining the haemodynamic response to exercise. Patients who develop symptoms during exercise, become hypotensive, manifest marked ST segment changes or develop ventricular arrhythmias are at high risk and should be considered for valve replacement [Chambers 1999; Amato *et al* 2001; Carabello 2002].

1.7.4 Symptomatic severe aortic stenosis

As soon as patients with severe aortic stenosis develop symptoms the treatment of choice is AVR because this substantially improves the quality of life and prognosis. In those patients declining valve surgery, or the frail elderly in whom major cardiac surgery would be inappropriate, palliation with conventional medical therapy, or in exceptional circumstances, balloon valvotomy are the only alternatives. Percutaneous AVR is a promising new technique that is currently under development in highly selected patient populations [Boudjemline and Bonhoeffer 2002; Cribier *et al* 2002].

1.7.5 Medical therapy

Breathlessness. Patients with evidence of pulmonary congestion may benefit from the judicious use of diuretics, vasodilators and positive ionotropic agents such as digoxin. Excessive use of diuretics should be avoided since patients with severe aortic stenosis often have diastolic dysfunction and depend on an adequate pre-load in order to maintain their cardiac output.

Despite the widespread belief that angiotensin-converting enzyme (ACE) inhibitors can cause dangerous hypotension in severe aortic stenosis, and are therefore contraindicated, there are little data to support this. From the limited literature available, two small studies demonstrated that first dose hypotension did not occur in patients with severe aortic stenosis, and that cardiac output and symptoms improved substantially [Grace *et al* 1991; Martinez-Sanchez *et al* 1996]. Although further study is required, some patients with heart failure and severe aortic stenosis could benefit from ACE inhibitors provided that they are carefully introduced in a hospital setting. Certainly those patients already established on therapy need not have it withdrawn since this may precipitate the onset of heart failure.

Digoxin can be helpful in the management of heart failure but should only be used in the presence of atrial fibrillation or where there is documented evidence of left ventricular systolic dysfunction. Atrial fibrillation is not well tolerated in the presence of severe stenosis and restoration to sinus rhythm (through electrical cardioversion or pharmacological cardioversion using amiodarone) should be attempted wherever possible.

Angina. In those individuals where angina is the predominant symptom, cautious use of beta-blockers and nitrates may be of benefit. Where coronary heart disease is suspected secondary prevention would be appropriate.

Syncope. Patients with syncope or pre-syncope should be further evaluated with a 24-hour cardiac monitor since aortic stenosis is commonly associated with atrioventricular block. There is no specific therapy for syncope unless it is caused by a bradyarrhythmia or tachyarrhythmia, where pacemaker insertion or antiarrhythmic therapy respectively should be considered.

1.7.6 BALLOON VALVOTOMY

Although balloon valvotomy plays an important role in the management of adolescents and young adults with aortic stenosis, it has largely been abandoned in older patients. The functional improvement obtained is limited, the re-stenosis and complication rates high, and the long-term outlook poor (<80% survival at 1 year) [Robicsek *et al* 1988; Bonow *et al* 1998]. On rare occasions, balloon valvotomy may play a role in patients with a limited life expectancy for other reasons, or as a bridge to AVR in critically ill patients with cardiogenic shock.

1.7.7 AORTIC VALVE REPLACEMENT

Aortic valve replacement incurs the virtual abolition of symptoms associated with improvements in physical functioning and quality of life, and a dramatic improvement in survival. Operative mortality in middle-aged adults is in the region of 5-8% [Linblom *et al* 1990; Sprigings and Forfar 1995; Kvidal *et al* 2000]; 5- and 10-year survival rates after aortic valve replacement are approximately 80% [Galloway *et al* 1990; Linblom *et al* 2000] and 65% respectively [Linblom *et al* 1990], and are similar to actuarial survival rates for the general population [Linblom *et al* 1990].

Factors associated with a higher operative mortality include increasing age [Sharony *et al* 2003], the presence of renal impairment, cerebrovascular and peripheral vascular disease [Gilbert *et al* 1999], the presence of impaired left ventricular function [Sharony *et al* 2003], and the need for simultaneous coronary artery bypass grafting [Sprigings and Forfar 1995]. Despite the increased operative risk associated with the presence of left ventricular failure, this is not an absolute contraindication to surgery. Indeed these patients may have most to gain from valve surgery in terms of improvements in prognosis.

1.7.8 AORTIC VALVE REPLACEMENT IN OCTOGENARIANS

Successful AVR is becoming increasingly common in patients over the age of eighty. Despite evidence suggesting that it should be offered to all suitable patients regardless of age, several studies have demonstrated a reluctance to refer older patients for valve surgery [Lindroos *et al* 1993; Abdul-Hamid and Mulley 1999; Bouma *et al* 1999]. This probably reflects both patient and physician misconceptions of the risks and benefits of operative intervention.

Although operative mortality is higher in octogenarians (nearer 5-15%), these individuals have almost as much to gain as their younger counterparts in terms of improved prognosis (5-year survival being 55-70%). Of perhaps greater importance is that the majority of survivors achieve a significant reduction in symptoms [Olsson *et al* 1992; Olsson *et al* 1996; Gilbert *et al* 1999; Sundt *et al* 2000; Kohl *et al* 2001] associated with a marked improvement in physical functioning and quality of life

[Olsson *et al* 1992; Sprigings and Forfar 1995; Olsson *et al* 1996; Sundt *et al* 2000]. Although intensive care [Gilbert *et al* 1999; Sundt *et al* 2000] and overall hospital stay [Olsson *et al* 1992; Sundt *et al* 2000; Kohl *et al* 2001] may be longer, the majority return to their own homes and retain their independence on discharge [Olsson *et al* 1992; Gilbert *et al* 1999]. However, post-operative complications are more common with a higher incidence particularly of stroke (4%) and acute renal failure (7-10%) [Sundt *et al* 2000]. In contrast with younger patients, octogenarians are usually offered a bioprosthetic (as opposed to a mechanical) valve, thus reducing the risk of valve thrombosis and anticoagulant associated haemorrhage.

1.7.9 Potential role for HMG CoA reductase inhibitors

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins are now well established in the primary and secondary prevention of coronary artery disease [Shepherd *et al* 1995; The Heart Protection Study Collaborative Group 2002]. Several studies have also shown that these drugs can cause regression of coronary artery disease [Zhao *et al* 1993] as well as reduce the calcific volume of coronary plaques [Callister *et al* 1998]. Given the clinical association of calcific aortic stenosis with hyperlipidaemia and coronary artery disease, and the striking histological similarities with atheroma, the speculation that statins may have the potential to influence disease progression in aortic stenosis is an intriguing hypothesis [Mohler 2000; Pearlman 2002].

Recent retrospective studies [Aronow *et al* 2001; Novaro *et al* 2001; Pohle *et al* 2001; Bellamy *et al* 2002; Shavelle *et al* 2002] have demonstrated that statins may

delay disease progression in aortic stenosis through their lipid-lowering and anti-inflammatory actions [Bellamy *et al* 2002]. These observational data should be interpreted with caution since none of these studies were randomised, and the statin doses were small. This preliminary evidence has been the rationale for establishing a randomised controlled trial of statin therapy in patients with aortic stenosis.

1.8 CONCLUSION

The need for an alternative to aortic valve surgery is highlighted by the increasing longevity of the population and rising prevalence of aortic stenosis. New therapeutic strategies to limit disease progression are needed in order to delay, and potentially avoid, the need for valve surgery.

1.9 AIMS AND HYPOTHESES

The aims of this thesis are to evaluate new methods of assessing and monitoring aortic stenosis, to clarify the factors that influence progression and outcome of aortic stenosis, and identify novel therapies for the disease. At the same time I sought to confirm the retrospective data suggesting that lipid-lowering therapy reduces coronary artery calcification.

The specific aims of the thesis were:

Chapter 3

In patients with calcific aortic stenosis;

1. to establish the validity and reproducibility of helical CT in the quantification of aortic valve calcium (AVC) burden.
2. to establish the reproducibility of echocardiographic measures of aortic stenosis severity.
3. to determine if there was a relationship between the severity of aortic valve stenosis determined by echocardiography and the degree of valvular calcification quantified by helical CT.

Hypothesis;

In patients with calcific aortic stenosis, aortic jet velocity, determined by echocardiography, correlates with the AVC score measured by helical CT.

Chapter 4

4. To conduct a randomised double-blind placebo-controlled trial of high dose lipid-lowering therapy in patients with calcific aortic stenosis in order to determine its effect on the progression of aortic stenosis and aortic valve calcification.

Hypothesis;

In patients with calcific aortic stenosis lipid-lowering therapy will halt the progression, or induce regression, of the valvular disease process. In particular, lipid-lowering therapy will:

(i) reduce the peak aortic jet velocity.

(ii) reduce the calcific volume of the aortic valve.

Chapter 5

5. To prospectively determine the effect of intensive lipid-lowering therapy on the progression of coronary artery calcification in patients with calcific aortic stenosis.

Hypothesis;

In patients with calcific aortic stenosis lipid-lowering therapy delays progression of coronary artery calcification.

Chapter 6

6. To identify prospectively traditional clinical risk factors and other novel predictors of cardiovascular risk, including inflammatory, vascular and cardiac markers that are associated with disease progression and clinical outcome in patients with calcific aortic stenosis.

Hypothesis;

In patients with aortic stenosis cardiovascular risk factors predict disease progression and clinical outcome.

CHAPTER 2

MATERIALS AND METHODS

2.1 INTRODUCTION

In this thesis, I have explored the interrelationship of atherosclerotic vascular disease and calcific aortic stenosis. This required a comprehensive assessment of valvular, myocardial and vascular variables. I have therefore measured valvular, myocardial and vascular structure and function in patients with calcific aortic stenosis. This has been complemented by the measurement of biochemical markers of systemic inflammation, and myocardial disease as well as non-invasive measures of vascular function such as arterial stiffness.

Echocardiography and CT are complementary methods of assessing the severity of aortic valve disease and its progression. Computed tomography also allows the measurement of coronary artery calcium, a marker of coronary artery disease, and pulse wave analysis provides a measure of arterial stiffness, a marker of peripheral arterial disease. These modalities have been used as the mainstay for the assessment of recruited patients.

2.2 THE SALTIRE TRIAL

The Scottish Aortic stenosis and Lipid lowering Therapy Impact on REgression (SALTIRE) trial was a prospective, randomised, double-blind placebo-controlled trial designed to assess the influence of high dose statin therapy on disease progression in patients with calcific aortic stenosis. It was funded by a project grant from the British Heart Foundation (PG/2000/044) and also supported by an

unrestricted educational grant award from Pfizer UK, and by the Wellcome Trust Clinical Research Facility in Edinburgh.

2.2.1 Definition of study population

Patients aged over 18 years with calcific aortic stenosis, an aortic jet velocity of at least 2.5 m/s, and aortic valve calcification on echocardiography were eligible for inclusion in the SALTIRE trial.

Exclusion criteria were child-bearing potential without contraception, active or chronic liver disease, a history of alcohol or drug abuse, severe mitral valve stenosis (mitral valve area, <1 cm^2), severe mitral or aortic regurgitation [Zoghbi *et al* 2003], significant left ventricular dysfunction (ejection fraction <35%), planned AVR, intolerance of statins, current statin therapy or a potential benefit from statin therapy (according to the treating physician), a baseline serum total cholesterol concentration of <4.0 mmol/L, and presence of a permanent pacemaker or cardiodefibrillator.

Of the patients screened, 455 were eligible for inclusion, 173 agreed to participate, and 155 ultimately underwent randomisation.

2.2.2 Study protocol and clinical follow-up

Between March 2001 and April 2002, the blinded study co-ordinator randomly assigned eligible patients by the minimisation technique [Treasure and MacRae 1998] with the use of a dedicated, locked computer program (Edinburgh University) incorporating the following eight variables: age, sex, smoking habit, hypertension,

diabetes mellitus, serum cholesterol concentration, aortic jet velocity, and aortic valve calcium score. Patients were assigned to either 80 mg of atorvastatin (Lipitor, Pfizer) or matched placebo as a single daily dose. Numbered containers were used.

Patients were assessed at baseline, at 2 and 6 months, and 6 monthly thereafter for a minimum of 2 years. The following clinical end-points were recorded throughout the study; cardiovascular and all cause mortality, AVR (whether for severe symptomatic stenosis or not), the development of symptoms attributable to severe aortic stenosis (confirmed by the patient's treating physician), and hospitalisation (both all cause and cardiovascular causes). Functional status and adverse events were recorded at each visit. Echocardiography and CT were performed annually.

2.3 BIOCHEMICAL VARIABLES

Fasting venous blood samples were taken annually. Samples for serum electrolytes, lipid profile and calcium concentrations were sent to the regional clinical laboratory for immediate analysis. Samples for estimation of serum brain natriuretic peptide (BNP) and C-reactive protein (CRP) concentrations were centrifuged at 4°C and stored at -80° C for later analysis.

2.3.1 INFLAMMATORY MARKERS

Serum CRP concentration is a sensitive but non-specific marker of systemic inflammation that is elevated in patients with vascular disease [Van der Meer *et al* 2002] and calcific aortic stenosis [Galante *et* al 2001]. It predicts clinical outcome in

patients with coronary heart disease and in apparently healthy subjects [Ridker *et al* 1998]. Plasma CRP concentrations were measured using a highly sensitive nephelometric assay with a monoclonal antibody to CRP coated on polystyrene beads (Dade Behring UK Ltd). The sensitivity of the assay was 0.175 mg/L, with intra-assay and inter-assay coefficients of variation of less than 5% [Chenillot *et al* 2000; Jialal *et al* 2001].

2.3.2 ENDOGENOUS CARDIAC HORMONES

Natriuretic hormones are endogenous cardiac hormones that are secreted from the cardiac atria and ventricles. Brain natriuretic peptide and its aminoterminal portion N-terminal BNP, are released in response to increased wall stretch and effect both natriuresis and diuresis with a resultant decrease in intravascular volume, blood pressure and pre-load. Serum concentrations are elevated in left ventricular dysfunction, and correlate with New York Heart Association (NYHA) class and prognosis [Tsutamoto *et* al 1997; McDonagh *et al* 2001; Berger *et al* 2002; Lubien *et al* 2002]. Serum BNP concentrations are also elevated in other structural heart disease [Nakamura *et al* 2002] including left ventricular hypertrophy and aortic stenosis. The N-terminal peptides are inactive and more stable [Boomsma *et* al 2001], and therefore N-terminal pro-BNP was measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, UK) on an Elecsys 2010 analyser. The sensitivity of the assay was 5 pg/mL, with intra-assay and inter-assay coefficients of variation of <5% [Hartman *et al* 2004].

2.4 ECHOCARDIOGRAPHY

Echocardiography, or cardiac ultrasound, relies on the processing of high frequency sound waves emitted from and received by an ultrasound transducer using a frequency of 2-5-MHz. It is a non-invasive and relatively quick technique to determine cardiac structure and function. There are three main modes of operation: M-mode (single-dimensional), two-dimensional, and Doppler (spectral Doppler and colour flow mapping). Spectral Doppler includes pulsed and continuous wave Doppler, which are used to assess velocity of blood flow and cardiac tissue at a given specific point. Colour flow mapping is superimposed on either one or two-dimensional images to provide a picture of blood flow using different colours for opposing directions of flow.

Echocardiography is the gold standard modality for the assessment of stenosis in patients with aortic valve disease and was the principal modality employed in this thesis.

2.4.1 SCANNING PROTOCOL AND TECHNIQUE

A single dedicated research sonographer, blinded to treatment allocation and CT results, performed all echocardiographic examinations and analyses. The echocardiograms were all performed on either an ATL-3000 (Philips Medical Systems (UK) Ltd, Stevenage, UK), or a Vingmed System 5 Performance (BMS (Scotland) Ltd, Belshill, UK) cardiac ultrasound machine using a 3-MHz transducer. Each patient was always scanned using the same equipment. All measurements were determined online, averaged from three cardiac cycles (five cycles if the patient was

in atrial fibrillation), and recorded onto super-VHS videotape and optical disk according to a standard protocol.

Aortic valve calcification was graded using the Rosenhek classification [Rosenhek *et al* 2000]. In the presence of calcification bicuspid valves are very difficult to diagnose using echocardiography, and diagnosis of a bicuspid valve was therefore only made if the appearance was unequivocal. In uncertain cases the valve was classified as tricuspid. Severity of aortic valve stenosis was determined using the peak aortic jet velocity, peak and mean aortic gradient, and AVA. Peak and mean aortic valve pressure gradients were calculated using the modified Bernoulli equation. Aortic valve area measured by the continuity equation requires measurement of left ventricular outflow tract velocity, peak aortic jet velocity and left ventricular outflow tract diameter.

Left ventricular outflow tract velocity was measured from an apical approach using pulsed Doppler just proximal to the aortic valve leaflets. Peak aortic jet velocity was determined using continuous wave Doppler from three sites; the apical long axis approach, the right upper sternal border, and the suprasternal notch using the stand alone probe, and the window generating the highest signal was recorded. Left ventricular outflow tract diameter (LVOTD) was measured in the parasternal long axis view in mid systole just below the aortic valve. It was measured at baseline and maintained constant throughout the study, given that LVOTD remains static over time and variation in the measurement of this dimension results in the greatest variability in valve area assessment [Myreng *et al* 1990].

The above measures of aortic stenosis severity have all been well validated when compared with invasive data, and as predictors of clinical outcome. Peak aortic jet velocity is the most reproducible measure, and is the strongest predictor of clinical outcome [Otto 2006].

2.5 COMPUTED TOMOGRAPHY

Computed tomography allows the generation of anatomical soft tissue images in the axial plane providing complementary data to echocardiography. Prior to the development of electron beam and helical CT, conventional CT was limited by slow scan times, and was therefore unsuitable for the assessment of rapidly moving cardiac structures. Helical CT, which only become widely available 5 years ago, has a gantry capable of continuous rotation and very rapid image acquisition. Technology has advanced dramatically since, such that with the introduction of multi-slice technology and ECG gating it is now possible to produce images virtually free of motion artefact. At the inception of the SALTIRE trial helical CT was the most advanced technology available.

Cardiac CT was initially introduced to look for the presence of coronary artery calcification as evidence of coronary atheroma, and subsequently to monitor disease progression in patients with coronary artery disease. Disease severity determined by invasive coronary angiography correlates well with coronary calcium burden assessed by both electron beam [Haberl *et al* 2001] and helical [Achenbach *et al*

2001; Nieman *et al* 2001] CT. In the late 1990's there was limited retrospective evidence that progression of coronary artery calcification may be delayed by the use of statin therapy [Callister *et al* 1998].

Aortic valve calcification is a common incidental finding on cardiac CT and although not diagnostic of aortic valve stenosis, the more heavily calcified the valve is the more likely it is that stenosis will be present [Lippert *et al* 1995]. Electron beam CT has only recently been validated as a reproducible technique for the quantification of AVC [Kizer *et al* 2001], and prior to the commencement of the SALTIRE trial the validity of helical CT had not been determined. Validation of helical CT was therefore an integral part of the SALTIRE trial, as well as the assessment of the relationship between the severity of aortic valve stenosis and calcium burden (see Chapter 3).

2.5.1 Scanning protocol and technique

Computed tomography was performed using a double-helix scanner (Twin II Flash; Philips Medical Systems (UK) Ltd, Stevenage, UK). The region of the aortic valve and coronary arteries was assessed using 2.7 mm slices, with a pitch of 0.7 and an increment of 1.4 mm during held inspiration. Computed tomography scanner quality assurance was performed before each examination with calibration against a standard phantom. A single research radiographer performed all scans, and a single consultant radiologist performed all analyses, both being blinded to the echocardiography results. Off-line analysis of the cardiac images was conducted using an automated, computerised software program (Picker Cardiac Scoring). This employs a modified

Agatston scoring method [Shemesh *et al* 1995] that uses a threshold of 90 Hounsfield Units (HU) to compensate for non-gated imaging. This modification produces comparable sensitivity and specificity to electron beam CT [Carr *et al* 2000]. Calcium scores were individually calculated for the aortic valve, and all three coronary arteries by summing the lesion scores for all sections containing calcium.

2.6 PULSE WAVE ANALYSIS

The link between blood pressure and cardiovascular disease has been clearly documented [Goldberg *et al* 1996]. Pulse wave analysis (PWA) by applanation tonography is a simple, non-invasive, reproducible method by which central aortic pressure waveforms can be determined from waveforms acquired peripherally at for example, the radial artery. The artery is compressed beneath the micromanometer probe tip, and arterial pressure is transmitted through the arterial wall to the sensor. Computer software calculates the central aortic pressure and waveform from the peripheral waveform using a generalised transfer function calibrated using peripheral blood pressure.

2.6.1 SCANNING PROTOCOL AND TECHNIQUE

Pulse wave analysis was performed at baseline and 6 monthly intervals thereafter. Patients were rested supine for 15 minutes prior to study. Radial PWA was performed using a high-fidelity applanation tonometer (Sphygmocor BPAS; PWV Medical, Sydney, Australia). After acquiring a series of consecutive waveforms, an averaged peripheral waveform was acquired and a generalised transfer function was

used to generate a central aortic pressure waveform from which the pulse pressure, augmentation pressure and augmentation index were determined. Two measurements of augmentation within 5 mmHg of each other were recorded on each occasion. Patients with atrial fibrillation were excluded, and recordings with poor quality waveforms were discarded: determined by visual inspection (SJC) with a minimum requirements in pulse height of >100 mmHg, diastolic variation of <5% and pulse height variation of <5%. Data on 105 patients were available at baseline, of these 20 patients had poor quality recordings and 9 patients were in atrial fibrillation, leaving a total of 84 patients for analysis.

2.7 DATA ANALYSIS AND STATISTICS

Computed tomography, BNP and CRP data were not normally distributed, and are expressed as median with interquartile ranges, or as mean with standard deviation (SD) after logarithmic transformation. Two-sided p values of less than 0.05 were considered to indicate statistical significance.

2.7.1 CHAPTER 3

2.7.1.1 *Reproducibility*

Reproducibility of echocardiographic and CT measures were determined by the method of Bland and Altman [Bland and Altman 1986] and expressed as the mean of the differences and the coefficient of repeatability (twice the standard deviation of the differences). As the difference of the two measures was proportional to their mean, the data for the AVC score underwent logarithmic transformation [Bland and Altman 1986]. Data were compared using regression analysis and analysis of

variance (ANOVA) using StatView version 5.0.1 (SAS Institute Inc., Cary, NC, USA). Where ANOVA demonstrated significant differences in responses, post-hoc comparisons were made using Fisher's protected least squares difference (PLSD) test (StatView version 5.0.1).

2.7.2 CHAPTER 4

2.7.2.1 *Progression of aortic valve disease*

The two primary end-points were progression of stenosis, determined according to changes in aortic jet velocity on Doppler echocardiography, and progression of valvular calcification, measured by CT. Secondary end-points were a composite of clinical end-points (death from cardiovascular causes, AVR, or hospitalisation attributable to severe aortic stenosis), AVR, death from any cause, hospitalisation for any cause, and hospitalisation for cardiovascular causes.

On the basis of standard deviations of 0.32 m/s per year [Faggiano *et* al 1992; Otto *et al* 1997] and 1100 arbitrary units (AU) per year [Shemesh *et al* 1995], we calculated that the planned sample size of 75 patients per group would give the study a power of 80% at a 5% significance level to detect a difference in the primary end-points of 0.15 m/s per year in aortic jet velocity and 500 AU per year in AVC score. These differences are equivalent to a reduction of more than 30% in the rate of progression of aortic stenosis. This would exclude a clinically significant effect in the majority of older patients with established disease, although a smaller effect may be clinically relevant in younger patients with mild aortic stenosis.

2.7.2.2 *Interim analysis and data monitoring committee*

The data monitoring committee conducted two interim assessments of safety and an interim assessment of efficacy one year after enrolment began. The trial was to be terminated early in the event of a negative effect of treatment (i.e. <0.05) or a strong benefit of treatment (i.e. $p<0.001$). On the recommendation of the data monitoring committee, the trial continued until the study was completed.

Analyses were performed using SPSS software, version 12.0, and SAS software, version 8e. Intention-to-treat analyses were used for all clinical outcome variables. Disease progression was determined primarily by dividing the change between the baseline and final scans by the duration of follow-up. Treatment comparisons for the continuous outcome variables were based on an analysis of covariance, with the pre-randomisation level of a variable used as a covariate. In a confirmatory analysis of the primary end-points, random coefficient models were fitted to incorporate all observations [Brown and Prescott 1999]. In the subgroup analyses, interaction terms between treatment and subgroup have been added to a model incorporating pre-randomisation level, treatment, and subgroup to identify factors that were associated with a differential treatment effect within subgroups. Categorical variables have been analysed using Fisher's exact test. Two-tailed tests were used throughout.

2.7.3 CHAPTER 5

2.7.3.1 *Progression of coronary disease*

Coronary artery calcium scores are expressed in AU based on the 130 HU threshold. The primary end-point, the rate of change of coronary calcium scores, was analysed

with random coefficient models [Bland and Altman 1986; Cowell *et* al 2005], after logarithmic transormation of the scores. In summarising the data, we calculated the change in coronary artery calcium scores by dividing the change between the baseline and final scores by the duration of follow-up. Rate of change in coronary calcium score is expressed as percentage change per year or as absolute change in the logarithm of the coronary artery calcium score.

2.7.4 CHAPTER 6

2.7.4.1 *Predictors aortic stenosis progression and clinical outcome*

Disease progression was determined by dividing the change between the baseline and final scans by the duration of follow-up. Clinical end-points were; cardiovascular and all cause mortality, AVR (whether for severe symptomatic stenosis or not), and the development of symptoms attributable to severe aortic stenosis (confirmed by the patient's treating physician). To define predictors of outcome patients who reached a clinical end-point were compared with those who did not.

Analyses were performed using SPSS software, version 12.0, and SAS software, version 8e. Predictors of progression were determined using regression analysis for continuous variables, and Chi-squared tests for categorical variables. Predictors of outcome were determined using Chi-squared tests for categorical variables, *t*-tests for continuous variables.

CHAPTER 3

AORTIC VALVE CALCIFICATION ON COMPUTED TOMOGRAPHY PREDICTS THE SEVERITY OF AORTIC STENOSIS

Based on

Cowell SJ, Newby DE, Burton J, White A, Northridge DB, Boon NA, Reid J.
Aortic valve calcification on computed tomography
predicts the severity of aortic stenosis.
Clin Radiol 2003;**58**(9):712-6.

3.1 SUMMARY

Background Disease progression in patients with aortic stenosis is more rapid in those with heavy calcification of the valve. The aims of this study were to determine the reproducibility of AVC scoring using helical CT, and to compare the AVC scores with the severity of valve stenosis measured by echocardiography.

Methods One hundred and fifty-seven patients aged 68 ± 11 years (range 34-85) with aortic valve stenosis underwent dual array helical CT and Doppler echocardiography performed by independent blinded observers. The AVC score was determined using automated computer software calibrated with a phantom.

Results Doppler echocardiography demonstrated a post-valve velocity of 3.45 ± 0.66 m/s and a peak gradient of 49 ± 11 mmHg. Computed tomography showed excellent reproducibility and the median score was 5858 (interquartile range 1555-14596) AU. The computed tomography AVC score positively correlated with the Doppler post-valve velocity and peak gradient ($r=0.54$, $p<0.0001$ for both) of the aortic valve. All patients with severe aortic stenosis had a calcium score of >3700 AU.

Conclusion Helical CT is a reproducible method of quantifying AVC burden. Calcification of the aortic valve is closely associated with the severity of aortic stenosis and heavy calcification suggests the presence of severe aortic stenosis that requires prompt cardiological assessment.

3.2 INTRODUCTION

Calcific aortic stenosis is the commonest reason for valve replacement in the developed world. The condition may be due to progressive calcification of a congenitally bicuspid valve or 'degenerative' calcification of a morphologically normal valve [Pomerance 1972]. Irrespective of the aortic valve morphology, the histological features are surprisingly similar to those of coronary atheroma and include lipid deposition, fibrosis and calcification [Otto *et al* 1994].

Disease progression in aortic stenosis is variable and unpredictable, but appears to be most rapid in patients with valvular calcification [Davies *et al* 1991; Bahler *et al* 1999]. The presence of AVC more than doubles the annual increase in aortic valve gradient (9.7 *versus* 4.4 mmHg/yr), and the echocardiographic grade of calcification correlates with the rate of disease progression [Davies *et al* 1991]. Indeed, moderate or severe aortic valve calcification is the strongest independent risk factor for an adverse clinical outcome with a 5-fold increase in the rate of death or AVR [Rosenhek *et al* 2000].

Computed tomography is being increasingly used as a non-invasive method of screening for atherosclerotic coronary artery disease [Breen *et al* 1992; Mautner *et al* 1994] with 80-100% sensitivity and 80% specificity [Harberl *et al* 2001]. There is an association between coronary artery disease and calcific aortic stenosis with approximately a third of patients with aortic stenosis having significant coronary stenoses on angiography [Mautner and Roberts 1992]. As a consequence, there have been several reports of

incidental aortic valve calcification detected during CT examinations with a prevalence of 10-30% [Woodring and West 1989; Lippert *et al* 1995]. However, there have been few reports [Lippert *et al* 1995] assessing the relationship between the degree of valvular calcification and the severity of aortic stenosis.

We wished to evaluate the reproducibility of helical CT in the quantification of AVC burden, and hypothesised that valvular calcification would correlate with the aortic post-valve velocity in patients with aortic stenosis.

3.3 METHODS

3.3.1 SUBJECTS

One hundred and fifty-seven patients being evaluated for the SALTIRE trial, participated in this substudy, which was undertaken with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each subject. Inclusion and exclusion criteria for the SALTIRE trial are outlined in Chapter 2. One patient, with a previous aortic root abscess, was excluded because of extensive aortic root calcification that obscured and prevented assessment of the aortic valve.

All patients underwent both echocardiography and CT within the month before randomisation to study therapy (atorvastatin 80 mg daily or placebo). Only pre-intervention baseline data are presented here.

3.3.2 ECHOCARDIOGRAPHY

The echocardiograms were performed on an ATL-3000 (Philips Medical Systems (UK) Ltd, Stevenage, UK) or a Vingmed System 5 Performance (BMS (Scotland) Ltd, Belshill, UK) cardiac ultrasound machine using a 3-MHz transducer for M-mode, and two-dimensional imaging with integral pulsed and continuous wave Doppler. The peak instantaneous aortic valve gradient was determined using the modified Bernoulli equation, and the AVA by the continuity equation. Aortic valve calcification was graded using the Rosenhek classification [Rosenhek *et al* 2000]. A single operator blinded to the results of the CT performed all echocardiographic examinations and analyses.

3.3.3 COMPUTED TOMOGRAPHY

The computed tomograms were performed using a dual array helical scanner (Twin II Flash; Philips Medical Systems (UK) Ltd, Stevenage, UK). The region of the aortic valve and coronary arteries was assessed using 2.7 mm slices, with a pitch of 0.7 and an increment of 1.4 mm during held inspiration. Operators blinded to the results of the echocardiogram performed all examinations and analyses. Computed tomography scanner quality assurance was performed prior to each examination with calibration against a standard phantom. Off-line analysis of the cardiac images was conducted using an automated, computerised software program (Picker Cardiac Scoring). This employs a modified Agatston scoring method [Shemesh *et al* 1995] that uses a threshold of 90 HU to compensate for non-gated imaging. This modification produces comparable sensitivity and specificity to electron beam CT. Calcium scores were individually

calculated for the aortic valve, and all three coronary arteries by summing the lesion scores for all sections containing calcium.

3.3.4 Reproducibility

Two unselected random samples of 20 subjects each were taken from the study population. Subjects underwent repeated CT or echocardiography within 4 weeks of the first examination and before administration of the study medication.

3.3.5 Data analysis and statistics

Data are expressed as mean ± SD. The calcium scores were not normally distributed and are expressed as median with interquartile ranges. The aortic valve and coronary artery calcium volume scores are expressed as AU). Reproducibility was assessed by the method of Bland and Altman [Bland and Altman 1986], and expressed as the mean of the differences and the coefficient of repeatability (twice the standard deviation of the differences). Since the difference of the two measures was proportional to their mean, the data for the aortic valve calcium score underwent logarithmic transformation [Bland and Altman 1986]. Data were compared using regression analysis and ANOVA using StatView *v*5.0.1 (SAS Institute Inc., Cary, North Carolina, USA). Where ANOVA demonstrated significant differences in responses, post-hoc comparisons were made using the Fisher's PLSD test (StatView *v*5.0.1). Statistical significance was taken at the 5% level.

3.4 RESULTS

Subject characteristics are shown in Table 3.1. In keeping with the study population, subjects were predominantly male, elderly and had haemodynamically significant aortic stenosis. Both echocardiography and CT showed excellent reproducibility (Table 3.2).

All but two patients had significant aortic valve calcification on CT (Figure 3.1). The median AVC score was 5858 AU. The majority of patients (107/157) had detectable coronary artery calcification that predominantly affected the left anterior descending (LAD) coronary artery. There was no correlation between the magnitude of the aortic valve and total coronary calcium scores ($r=0.04$, $p=0.61$).

3.4.1 COMPARISON BETWEEN ECHOCARDIOGRAPHY AND COMPUTED TOMOGRAPHY

Echocardiographic grade of calcification correlated weakly with the computed tomography AVC score ($r=0.29$, $p<0.001$) and the peak aortic jet velocity ($r=0.40$, $p<0.001$). The aortic valve calcium score correlated strongly with the peak aortic jet velocity ($r=0.54$, $p<0.0001$: $y=0.00004x +3.09$; Figure 3.2) and the mean ($r=0.54$, $p<0.0001$: $y=0.0008x +20.7$) and peak gradient ($r=0.54$, $p<0.0001$: $y=0.0013x +39.1$) of the aortic valve, but only weakly correlated with the aortic valve area ($r=0.20$, $p=0.01$).

TABLE 3.1 Baseline characteristics

Baseline subject characteristics		
Number	157	
Age	68 ± 11	years
Sex	71 %	male
Bicuspid Aortic Valve	5	
Atrial Fibrillation	11	
Echocardiogram		
Pre-valve velocity	1.08 ± 0.22	m/s
Post-valve velocity	3.45 ± 0.66	m/s
Peak gradient	49 ± 19	mmHg
Mean gradient	27 ± 11	mmHg
Valve area	1.02 ± 0.40	cm^2
Computed Tomogram*		
Aortic Valve	5858 (1555-14596)	AU
Coronary Artery		
LAD	97 (0-603)	AU
Circumflex	0 (0-36)	AU
Right	0 (0-0)	AU
Total	121 (0-731)	AU

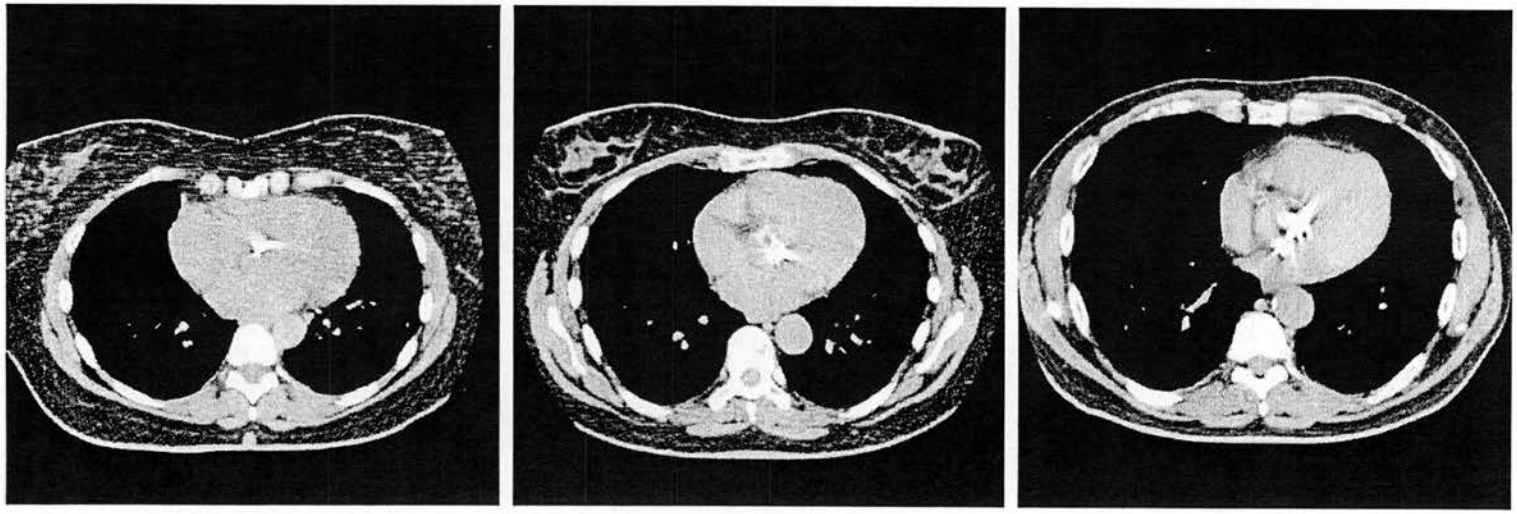
Mean ± SD.
***Median (interquartile range).**
LAD - left anterior descending.

TABLE 3.2 Reproducibility of echocardiographic and computed tomographic assessments of the aortic valve (n = 20)

	Mean	Mean of Difference	Standard Deviation of Differences	Coefficient of Repeatability	
Echocardiogram					
Post-valve velocity	3.20 ± 0.11	0.00	0.16	0.32	m/s
Peak gradient	41.7 ± 3.0	0.0	4.1	8.2	mmHg
Mean gradient	21.6 ± 1.8	0.2	3.8	7.6	mmHg
Valve area	1.17 ± 0.10	0.06	0.39	0.78	cm^2
Computed Tomogram*					
Valve Calcium Score	3.86 ± 0.49	0.01	0.04	0.07	PAU

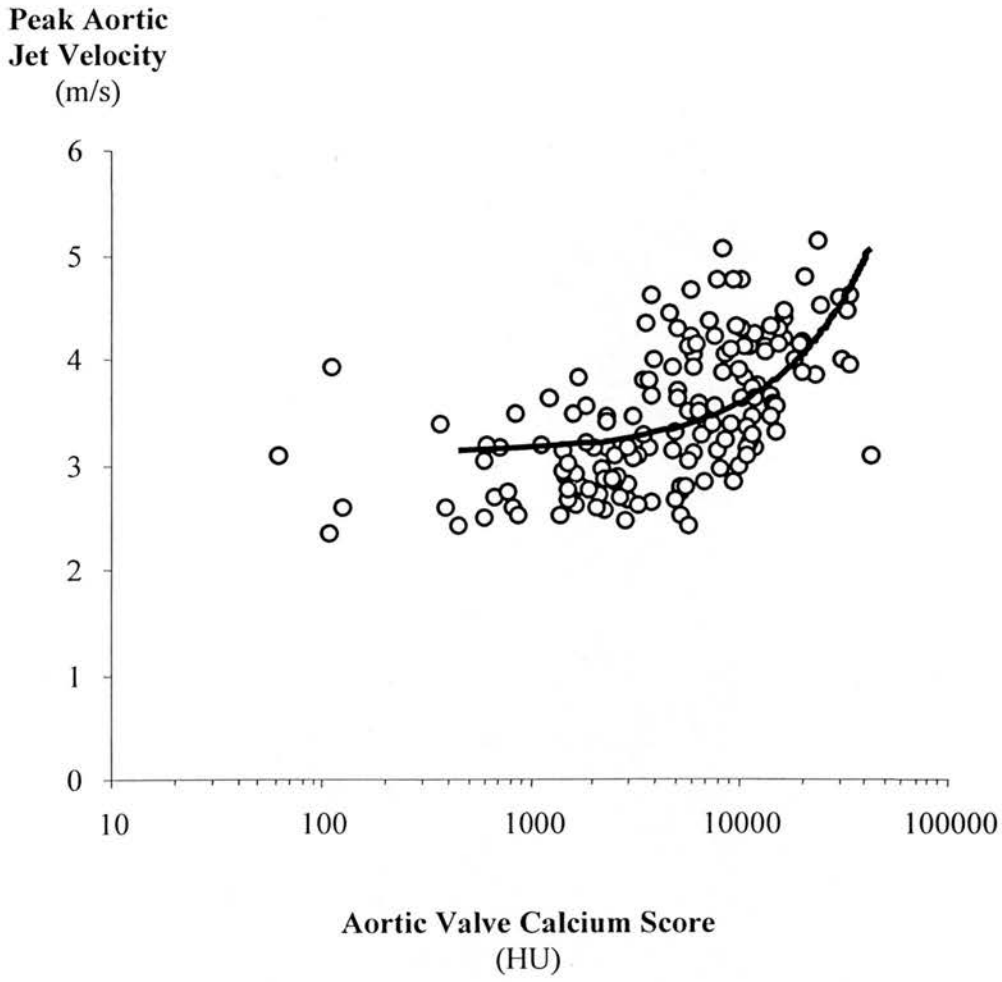
***Aortic valve calcium score has undergone logarithmic transformation.**

Figure 3.1 Representative computed tomograms showing mild, moderate and severe calcification of the aortic valve.



Mild Moderate Severe

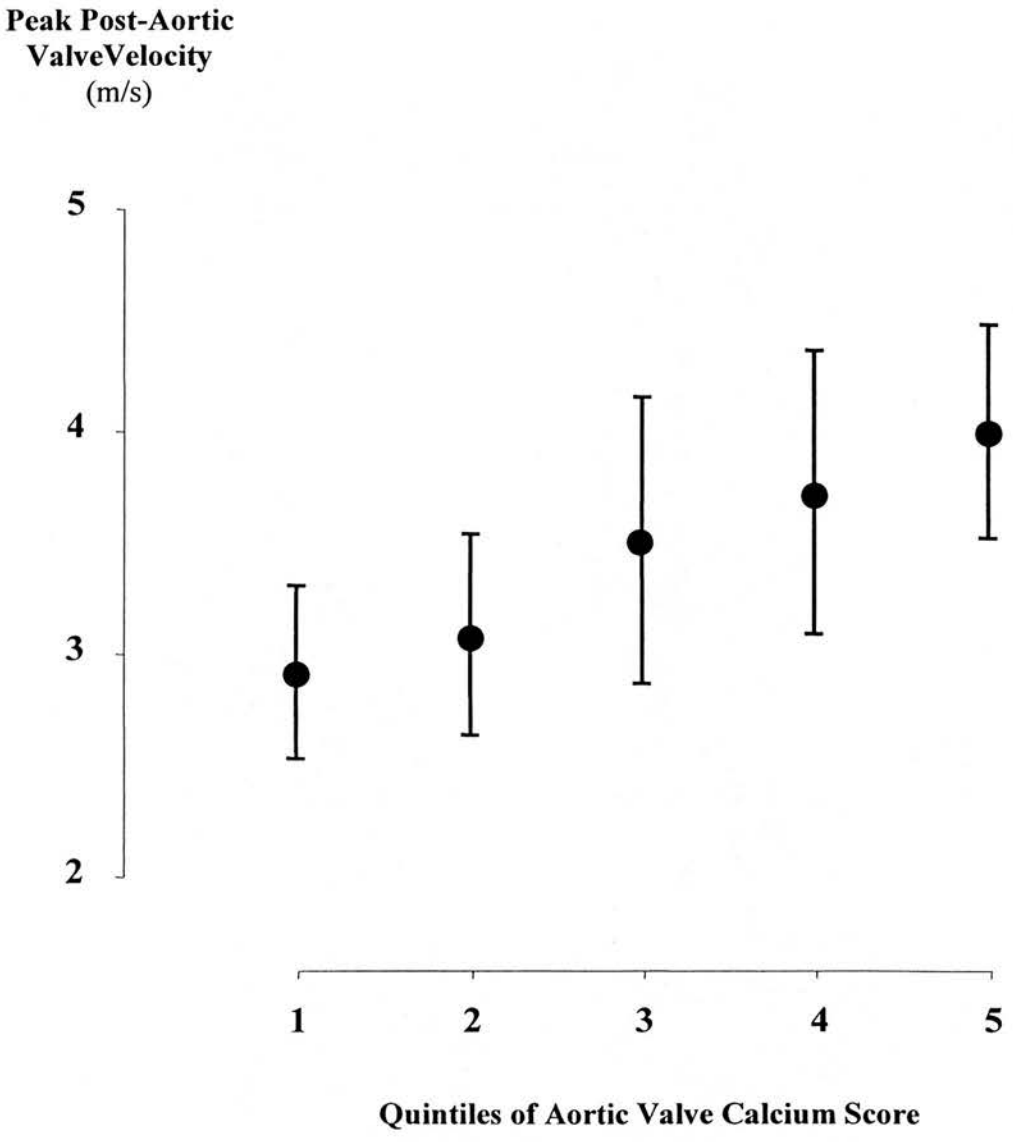
Figure 3.2 **Correlation of aortic valve calcification and peak aortic jet velocity.**



r=0.54, p<0.001.
HU - Hounsfield Units.

Stratifying the patients according to the quintiles of calcification demonstrated a progressive increase in the mean peak aortic jet velocity (Figure 3.3). All patients with severe aortic valve stenosis (peak aortic jet velocity >4 m/s) had an AVC score of >3700 AU. This threshold gives a sensitivity of 100% and specificity of 50% that translates into a negative predictive value of 100% and a positive predictive value of 39% for the detection of severe aortic stenosis. A threshold of 6000 AU gives a sensitivity of 90% and specificity of 66% giving a negative predictive value of 95% and a positive predictive value of 45%.

Figure 3.3 **Mean (± SD) peak aortic jet velocity in the quintiles of aortic valve calcification.**



ANOVA, $p<0.001$. Fisher's PLSD test, $p\leq0.03$ for all comparisons between the individual quintiles except quintile 1 *versus* quintile 2, and quintile 3 *versus* quintile 4.
PLSD - protected least squares difference.

3.5 DISCUSSION

In patients with aortic stenosis, we have demonstrated that helical CT is a reproducible means of quantifying AVC burden. We have also established a close association between the degree of aortic valve calcification and the haemodynamic severity of aortic stenosis. In particular, the presence of severe and potentially critical aortic stenosis is associated with heavy calcification. We suggest that patients found to have incidental aortic valve calcification on CT require further cardiological assessment for aortic stenosis, especially when there is heavy calcification.

Recent studies have evaluated electron beam CT in the quantification of AVC burden, revealing an interscan variability of less than 10% [Pohle *et al* 2001; Budoff *et al* 2002]. Here we have confirmed that helical CT also provides accurate quantification of valvular calcification, with sufficient accuracy to evaluate progression of calcium accumulation over time. Further studies are required to determine whether different modes of CT image acquisition are comparable.

This is the first study to compare AVC scores with echocardiogram-derived measures of valvular gradients in a large number of patients with aortic stenosis. One previous small study of 19 patients also suggested that there might be an association between the severity of aortic stenosis and the valvular calcium score [Kizer *et al* 2001]. We have studied a much larger population with sufficient power to demonstrate a marked correlation between these parameters. However, because of the selected study

population, these findings should only be cautiously extrapolated to aortic valve calcification identified during general population screening or as an incidental finding. A recent retrospective study suggested a 20% incidence of aortic valve calcification in over 2,000 patients attending for detection of coronary calcification [Kizer *et al* 2001]. One retrospective study of 109 such patients who had undergone both CT and echocardiography, reported a 30% prevalence of aortic valve calcification in which aortic stenosis was documented in 15% [Lippert *et al* 1995]. In the absence of aortic valve calcification, none of the patients had significant aortic valve stenosis. In the current study, only 2 patients (1%) had no detectable valvular calcification suggesting an excellent negative predictive value. Our study findings additionally suggest that the likelihood of significant valvular stenosis increases with the severity of calcification.

Echocardiography is the mainstay of clinical monitoring for aortic valve stenosis but provides only a subjective and semi-quantitative measure of aortic valve calcification. Computed tomography provides a more accurate method of quantifying calcium that more closely correlates with the aortic valve gradient than echocardiography-derived measures of calcification. It may be useful to quantify more accurately the degree of calcification given that it is the strongest independent risk factor for disease progression and an adverse clinical outcome [Rosenhek *et al* 2000]. Further prospective studies are now needed to assess whether the degree of calcification [Pohle *et al* 2001] provides useful additional clinical information that would help guide patient management. Indeed, it has been suggested that patients with severe aortic stenosis and marked calcification should undergo AVR even in the absence of symptoms [Rosenhek *et al* 2000].

Aortic valve calcification is associated with an increased cardiovascular mortality [Otto *et al* 1999; Rosenhek *et al* 2000]. The underlying pathogenetic process appears to share many of the features and risk factors for atherosclerosis [Otto *et al* 1994] including hypercholesterolaemia, [Wilmshurst *et al* 1997; Chui *et al* 2001] that is associated with a more rapid progression of aortic valve calcification [Pohle *et al* 2001]. There are several studies, including the SALTIRE trial, that are assessing the impact of lipid-lowering therapy on the rate of progression of aortic stenosis. Given that statin use is associated with halting the progression of coronary calcification [Callister *et al* 1998], the present study indicates that helical CT is a valuable method of assessing aortic valve calcification and disease progression in such intervention trials. Indeed, one preliminary observational study has suggested that statin use is associated with a lower rate of progression of aortic valve calcification [Shavelle *et al* 2002].

Using our methodology, we have found a close correlation between echocardiographic measures of aortic stenosis and AVC scores measured by multi-slice helical CT. The applicability of our findings to the latest CT scanners with differing specifications such as 64 slice multidetector array acquisition, or imaging parameters, such as slice thickness, pitch and ECG gating, is unknown. However, there is a high degree of agreement between different machines and coronary calcium scores [Carr *et al* 2000], and we believe that our findings will be applicable to other CT equipment. The reference ranges of the AVC scores are likely to be dependent on the imaging protocol and CT equipment used. However, broadly speaking, poorly defined or diffuse segments of

calcium usually represent a minor aortic valve gradient. In contrast, coalescent calcium centred on the aortic valve is likely to represent moderate stenosis where as very heavy calcification almost invariably represents a significant degree of valvular stenosis (Figure 3.1).

In conclusion, quantification of aortic valve calcification by helical CT is a reproducible technique. Calcification of the aortic valve is closely associated with the severity of aortic stenosis and heavy calcification suggests the presence of severe aortic stenosis that requires prompt cardiological assessment. Patients with lesser degrees of aortic valve calcification should be screened for aortic stenosis and monitored for disease progression.

CHAPTER 4

INTENSIVE LIPID-LOWERING THERAPY DOES NOT HALT THE PROGRESSION OF CALCIFIC AORTIC STENOSIS

Based on

Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA. Scottish Aortic Stenosis and Lipid-Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomised trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;**352**(23):2389-97.

4.1 SUMMARY

Background Calcific aortic stenosis has many characteristics in common with atherosclerosis including hypercholesterolaemia. We hypothesised that intensive lipid-lowering therapy would halt the progression or induce regression of calcific aortic stenosis.

Methods In this double-blind placebo-controlled trial, patients with calcific aortic stenosis were randomised to either atorvastatin 80 mg daily or matched placebo. Aortic valve stenosis and calcification were assessed using Doppler echocardiography and helical CT respectively. The primary end-points were change in aortic jet velocity and AVC score.

Results Seventy-seven patients were assigned to atorvastatin and 78 to placebo with a median follow-up of 25 months (range 7-36). Serum low-density lipoprotein cholesterol concentration remained at 3.4 ± 0.8 mmol/L in the placebo group, and fell to 1.7 ± 0.6 mmol/L in the atorvastatin group ($p<0.001$). Increase in aortic jet velocity was 0.199 ± 0.210 m/s per year in the atorvastatin group, and 0.203 ± 0.208 m/s per year in the placebo group ($p=0.95$: difference 0.002; 95% confidence interval (CI), -0.066 to 0.070 m/s/yr). Progression in valvular calcification was 22.3 ± 21.0% per year in the atorvastatin group and 21.7 ± 19.8% per year in the placebo group ($p=0.93$: ratio of post-treatment AVC score: 0.998; 95% CI, 0.947 to 1.050).

Conclusion This is the first double-blind randomised controlled trial of lipid-lowering therapy in patients with calcific aortic stenosis. It has clearly demonstrated that whilst

high dose atorvastatin more than halves serum LDL cholesterol concentrations, it does not halt the progression or induce regression of the valvular disease process.

4.2 INTRODUCTION

In the western world, calcific aortic stenosis is the commonest form of valvular heart disease and its incidence increases with age such that 3% of adults over 75 years of age have aortic stenosis [Stewart *et al* 1997]. It is a gradually progressive disease, characterised by a long asymptomatic phase lasting several decades, followed by a shorter symptomatic phase associated with severe narrowing of the aortic valve orifice. Once symptoms occur, the prognosis is poor and usually mandates surgery. Calcific aortic stenosis is now the leading indication for valve replacement in North America and Europe. However, there are currently no effective disease modifying treatments and the possibility of halting, or even inducing regression of, the disease process would represent a major therapeutic advance.

Calcific aortic stenosis is mediated by a chronic active inflammatory disease process that has many similarities with atherosclerosis and includes infiltration of inflammatory cells, lipoproteins, lipids, extracellular bone matrix proteins and bone mineral [Olsson *et al* 1994; Otto *et al* 1994; O'Brien *et al* 1996; Olsson *et al* 1999]. Consistent with these observations, clinical studies have revealed a strong association with coronary artery disease [Mautner and Roberts 1992; Peltier *et al* 2003] and many of its risk factors including hypercholesterolaemia [Stewart *et al* 1997]. Disease progression in aortic

stenosis is variable and is influenced by several factors including degree of stenosis [Otto *et al* 1997], valvular calcification [Davies *et al* 1991; Bahler *et al* 1999; Rosenhek *et al* 2000] and hypercholesterolaemia [Palta *et al* 2000; Nassimiha *et al* 2001]. Indeed, calcific aortic stenosis is a feature of severe homozygous familial hypercholesterolaemia [Rallidis *et al* 1998] and intensive lipid-lowering therapy with plasmapheresis has been reported to regress valvular stenosis in these patients [Keller *et al* 1986].

Hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, are now established treatments for the primary and secondary prevention of coronary artery disease [Shepherd *et al* 1995; The Heart Protection Study Collaborative Group 2002]. Several studies have shown that these drugs can halt the progression of coronary artery disease [Zhao *et al* 1993; Jukema *et al* 1995; Pitt *et al* 1995] as well as reduce the calcific volume of coronary plaques [Callister *et al* 1998; Budoff *et al* 2000; Achenbach *et al* 2002]. Given the clinical association with hypercholesterolaemia and coronary artery disease, and the striking histological similarities with atheroma, it has been suggested that statin therapy may halt the progression, or even induce regression, of calcific aortic stenosis. This hypothesis is supported by numerous retrospective observational studies [Arnow *et al* 2001; Novaro *et al* 2001; Pohle *et al* 2001; Bellamy *et al* 2002; Shavelle *et al* 2002; Rosenhek *et al* 2004] showing that concomitant statin therapy was associated with a delay in the progression of the aortic jet velocity of 0.30 m/s per year and calcification by 30% per year.

The aim of the SALTIRE trial was to establish whether intensive lipid-lowering therapy with atorvastatin 80 mg daily would halt the progression, or induce regression, of the aortic jet velocity on Doppler echocardiography, and the AVC score on CT, in patients with calcific aortic stenosis.

4.3 METHODS

The SALTIRE trial was a randomised double-blind placebo-controlled trial. The investigation conformed to the Declaration of Helsinki, and all participating regional ethics committees approved the study protocol. All patients gave written informed consent.

4.3.1 PATIENT POPULATION

Patients from the south-east of Scotland attending seven district and two regional centres were approached for enrolment by the study co-ordinator between December 2001 and April 2002. Eligible individuals were identified from outpatient clinics and echocardiography databases. Those aged over 18, with calcific aortic stenosis, an aortic jet velocity of ≥2.5 m/s, and grade 1-3 calcification of the aortic valve on echocardiography [Rosenhek *et al* 2000] were included. Exclusion criteria are detailed in Chapter 2. Of the patients screened, 455 were eligible for inclusion, 173 agreed to participate and 155 were ultimately randomised to treatment.

4.3.2 STUDY PROTOCOL

Between March 2001 and the end of April 2002, the blinded study co-ordinator randomised 155 eligible patients by the minimisation technique [Treasure and MacRae 1998] using a dedicated locked computer programme (Edinburgh University) which incorporated eight baseline variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, aortic jet velocity, and AVC score. Patients were assigned to either atorvastatin 80 mg daily or matched placebo (Pfizer Ltd, UK) as a single daily dose using numbered containers.

Patients were assessed at baseline, 2 months, 6 months and every 6 months thereafter for between 2 and 3 years. Clinical evaluation included assessment of functional status and adverse events as well as blood analysis of renal function, liver function, creatine kinase and lipid profile. Echocardiography and CT were performed at baseline, at each annual visit and prior to withdrawal from the study. Randomised patients who were subsequently commenced on open label statin therapy by their attending physician were immediately scanned and then withdrawn from the study.

4.3.2.1 *Echocardiography*

Assessment of valvular stenosis was determined by a single dedicated research ultrasonographer. All scans were performed on one of two dedicated ultrasound machines Vingmed System 5 Performance (BMS (Scotland) Ltd, Belshill, UK), or ATL-3000 cardiac ultrasound machine (Philips Medical Systems (UK) Ltd, Stevenage, UK)

that were maintained constant for each patient throughout the study. Patients were studied using a 3-MHz transducer for M-mode, and two-dimensional imaging with integral pulsed and continuous wave Doppler. All measurements were determined on-line, averaged from three cardiac cycles (five cycles if in atrial fibrillation), and recorded onto Super-VHS video and optical disk using a standardised proforma. Aortic jet velocity was recorded from the window generating the highest signal (apical, right parasternal or suprasternal). Left ventricular outflow tract velocity was measured from an apical approach just proximal to the aortic valve leaflets. Peak and mean aortic valve gradients were calculated using the Bernoulli equation, and AVA using the continuity equation. The left ventricular outflow tract diameter was measured at baseline and maintained constant throughout the study.

4.3.2.2 *Computed tomography*

Computed tomography was performed by a single operator using a double-helix scanner (Twin II Flash; Philips Medical Systems (UK) Ltd, Stevenage, UK) and calibrated against a standard phantom. The region of the aortic valve was imaged with a spiral acquisition using 2.7 mm slices, with a pitch of 0.7 and an increment of 1.4 mm during held inspiration. All images were analysed by a single operator using an automated computerised software program (Picker Cardiac Scoring). This employs a modified Agatston scoring method [Shemesh *et al* 1995] that uses a threshold of 90 HU to compensate for non-gated imaging.

Reproducibility of echocardiographic and CT assessments was determined in two subsets of 20 patients as described in Chapter 3 [Cowell *et al* 2003]. Coefficients of reproducibility for aortic jet velocity and AVC score were 0.32 m/s and 0.07 pAU respectively [Cowell *et al* 2003].

4.3.3 DATA AND STATISTICAL ANALYSIS

The study was designed to assess the two primary end-points: progression of stenosis determined by change in aortic jet velocity on Doppler echocardiography, and progression of valvular calcification measured by CT. Secondary end-points were a composite clinical end-point (cardiovascular mortality, AVR) or hospitalisation attributable to severe aortic stenosis), AVR, all cause hospitalisation and cardiovascular hospitalisation. The planned sample size of 75 patients per group gave 80% power at a 5% significance level to detect a difference in the primary end-points of 0.15 m/s per year in aortic jet velocity [Faggiano *et al* 1992; Otto *et al* 1997] and 500 AU in the AVC score [Shemesh *et al* 1995].

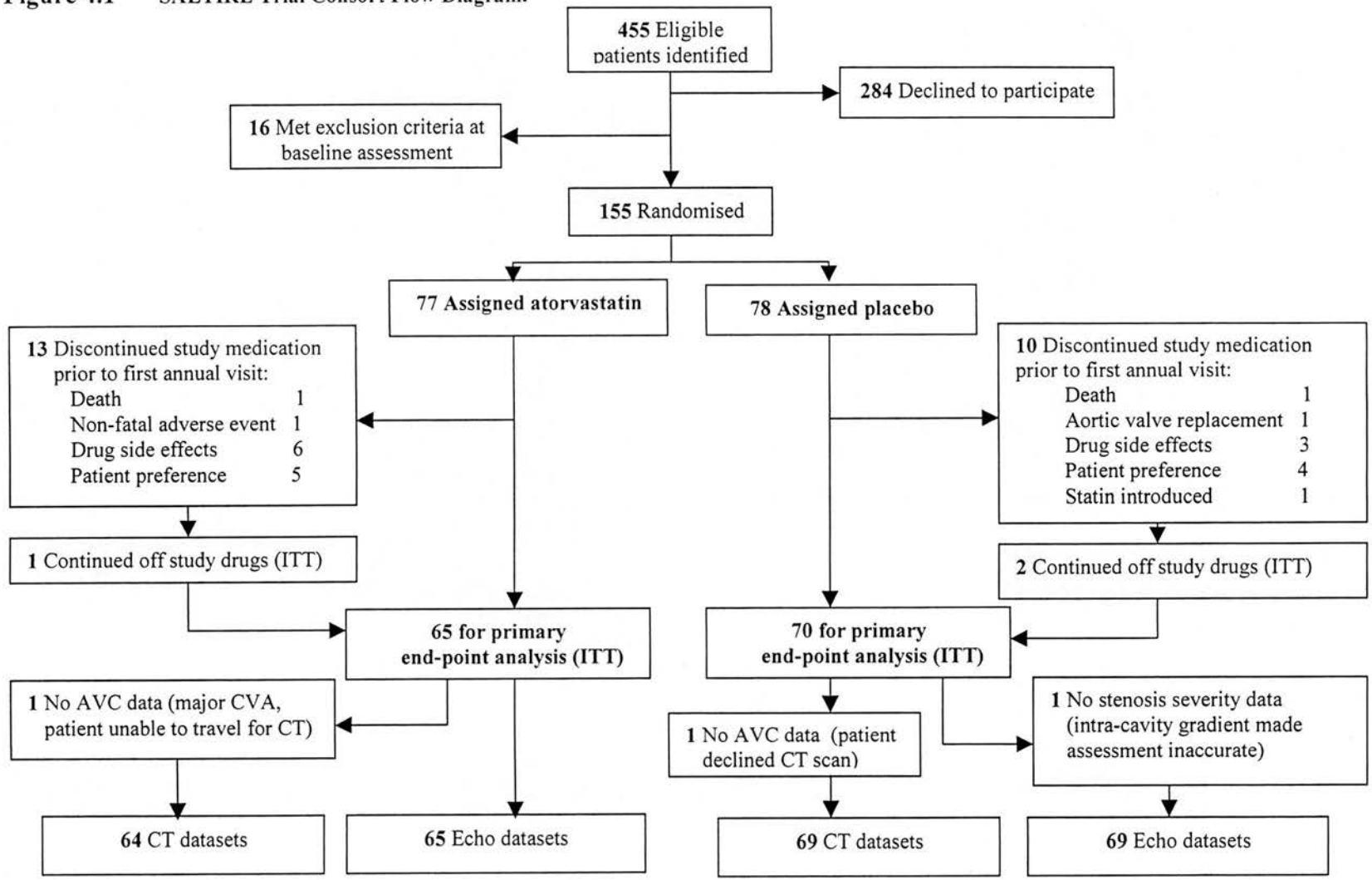
The Data Monitoring Committee conducted two interim assessments of safety, as well as an interim assessment of efficacy one year after randomisation. The trial was to be terminated early in the event of a negative treatment effect ($p<0.05$), or strong treatment benefit ($p<0.001$). On the recommendation of the Data Monitoring Committee, the trial continued until study completion.

Analyses were performed by RP using SPSS Version 12.0. All outcome variables were analysed by intention-to-treat. Disease progression was determined by calculating the rate of change between the baseline and final scans. Treatment comparisons for the continuous outcome variables were based on an analysis of covariance, with the pre-randomisation level of that variable used as a covariate. In the subgroup analyses, interaction terms between treatment and subgroup have been added to a model incorporating pre-randomisation level, treatment and subgroup to assess whether there is any evidence of a differential treatment effect in subgroups. Categorical variables have been analysed using Fisher's exact test. Two-tailed tests are employed throughout. Statistical significance was taken as $p<0.05$.

4.4 RESULTS

Seventy-seven patients were assigned to atorvastatin and 78 to placebo with a median follow-up of 25 months (range 7-36) (Figure 4.1). As a consequence of minimisation, the baseline characteristics were well matched (Table 4.1). All patients had good left ventricular function except one patient who had mild impairment of systolic function. Mean aortic jet velocity was 3.43 ± 0.64 (range 2.5-5.0) m/s, and median AVC score was 5920 (interquartile range 2485-14231) AU. There were 119 patients with mild to moderate aortic stenosis (aortic jet velocity, 2.5 to 3.9 m/s), and 36 with severe stenosis (aortic jet velocity, ≥4.0 m/s).

Figure 4.1 **SALTIRE Trial Consort Flow Diagram.**



ITT - intention-to-treat; AVC - aortic valve calcium; CVA - cerebrovascular accident; CT - computed tomography.

TABLE 4.1 Baseline characteristics

	Atorvastatin n = 77	Placebo n = 78
Demographics		
Age (years)	68 (11)	68 (10)
Sex (% male)	68	72
Cardiovascular Risk Factors		
Hypertension	48	54
Hyperlipidaemia	8	5
Diabetes mellitus	3	4
Current smoker	21	22
Cardiovascular Disease		
Coronary heart disease	18	21
Cerebrovascular disease	9	11
Peripheral vascular disease	5	13
Drug History		
Aspirin	43	40
ACE inhibitor	12	14
Beta-blocker	21	27
Warfarin	8	12
Physical Examination		
Height (cm)	168 (9)	169 (8)
Weight (Kg)	79 (15)	80 (15)
Heart rate (bpm)	68 (11)	66 (12)
Systolic blood pressure (mmHg)	144 (18)	144 (21)
Diastolic blood pressure (mmHg)	82 (10)	81 (12)
Biochemistry		
Total cholesterol (mmol/L)	5.8 (1.0)	5.7 (0.9)
LDL cholesterol (mmol/L)	3.6 (0.9)	3.5 (0.8)
Cholesterol:HDL ratio	4.1 (1.1)	4.1 (1.4)
Urea (mmol/L)	6.1 (2.1)	6.9 (6.8)
Creatinine (μmol/L)	91 (21)	92 (22)
Glucose (mmol/L)	5.2 (1.1)	5.4 (1.2)
Electrocardiogram		
Sinus rhythm	94	92
Atrial fibrillation	6	8
Romhilt-Estes score†	1 (0-3)	2 (1-4)
Echocardiography		
Tricuspid aortic valve	96	97
Bicuspid aortic valve	4	3
Aortic jet velocity (m/s)	3.39 (0.62)	3.45 (0.67)
Peak gradient (mmHg)	47.8 (17.4)	49.5 (19.5)
Aortic valve area (cm^2)	1.03 (0.4)	1.02 (0.41)
Computed Tomography		
Aortic valve calcium score†	5424 (2750-9689)	6221 (3037-9575)
Log aortic valve calcium score (LogAU)	3.7 (0.5)	3.7 (0.6)

Continuous variables given as mean (SD). Categorical variables expressed as per cent.
† Median (interquartile range).
ACE - angiotensin-converting enzyme; bpm - beats per minute; LDL - low-density lipoprotein; HDL - high-density lipoprotein; Log - logarithm.

4.4.1 SERUM CHOLESTEROL CONCENTRATIONS

The mean serum low-density lipoprotein cholesterol concentration remained at 3.4 ± 0.8 mmol/L in the placebo group, and fell to a mean on treatment of 1.7 ± 0.6 mmol/L in the atorvastatin group ($p<0.001$). This equates to a 53% reduction in LDL cholesterol in the atorvastatin group (Figure 4.2c). Serum total cholesterol was 5.5 ± 0.9 mmol/L and 3.5 ± 0.7 mmol/L in the placebo and atorvastatin groups respectively ($p<0.001$) and is in keeping with pill count compliance that averaged 97% in both treatment groups.

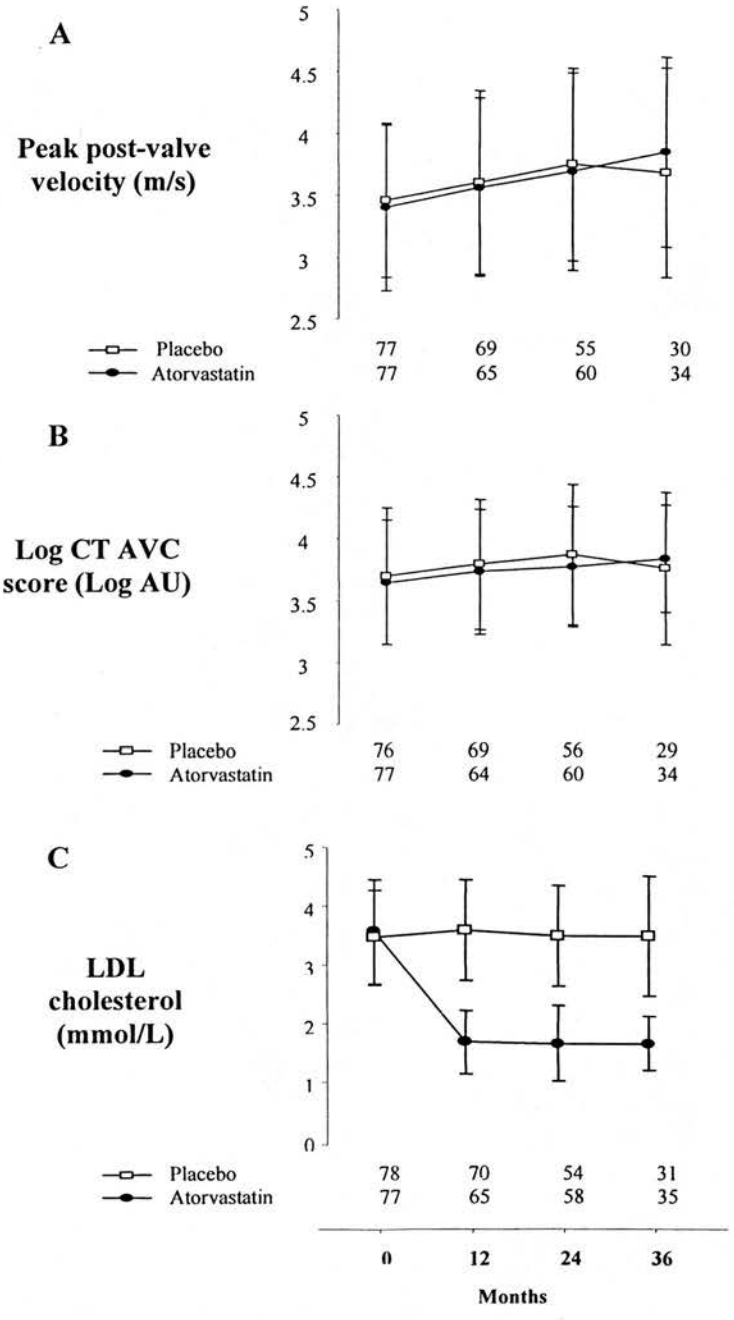
4.4.2 IMPACT OF ATORVASTATIN ON DISEASE PROGRESSION

Intensive lipid-lowering therapy with atorvastatin 80 mg daily had no effect on the rate of change in aortic jet velocity or valvular calcification (Table 4.2; Figure 4.2). Serum LDL cholesterol concentrations did not correlate with disease progression on echocardiography ($r=0.021$, $p=0.81$) or CT ($r=-0.109$, $p=0.21$) (Figure 4.3). The proportion of patients reaching secondary clinical end-points appeared to be fewer in the atorvastatin group but none of the comparisons achieved statistical significance (Table 4.3).

4.4.3 SUBGROUP ANALYSES

Pre-specified subgroup analysis of the primary end-point data was conducted in patients with mild to moderate (aortic jet velocity of <4.0 m/s) and severe (aortic jet velocity ≥4.0 m/s) aortic stenosis at baseline. As anticipated from earlier studies, patients with

Figure 4.2 **Progression in aortic valve stenosis and serum LDL cholesterol concentrations in patients treated with atorvastatin 80 mg daily (solid circles) and matched placebo (open squares).**



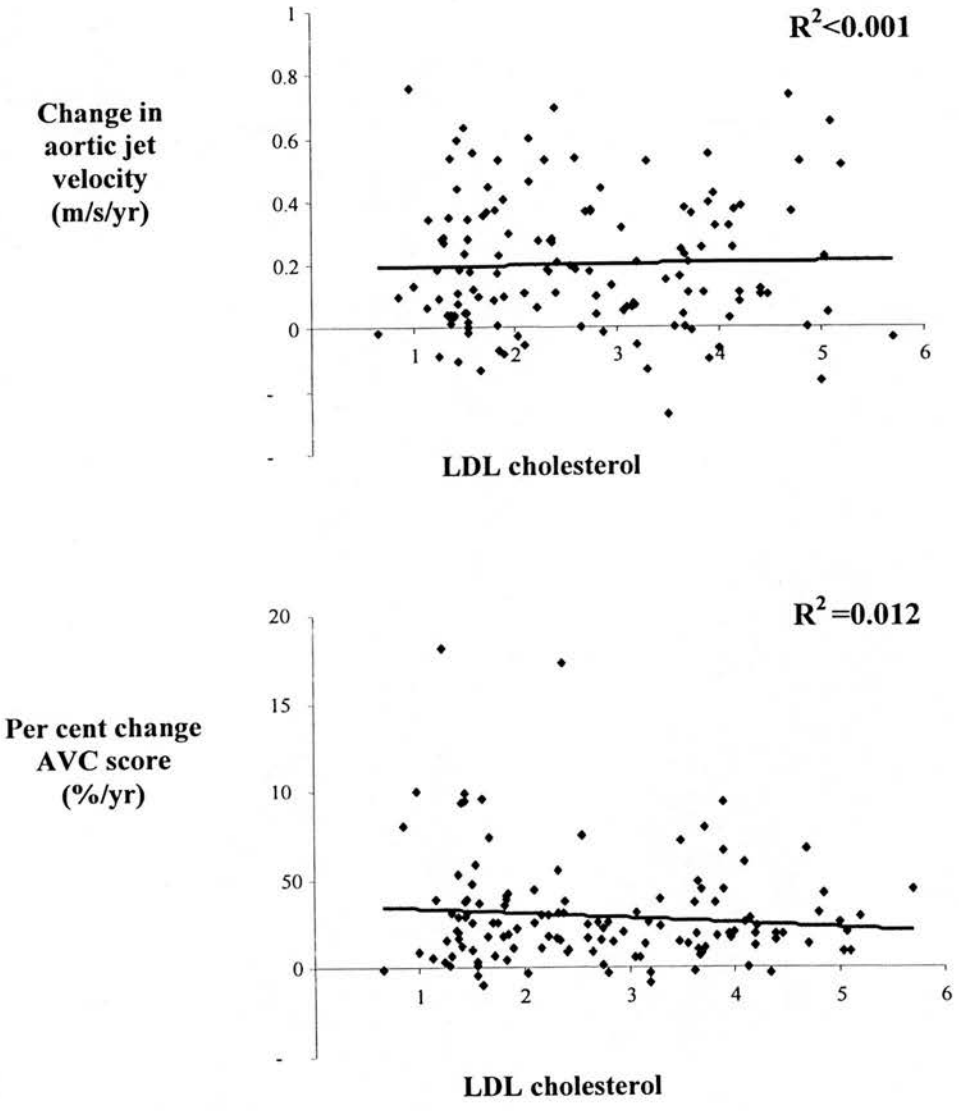
LDL – low-density lipoprotein; CT - computed tomography; AVC - aortic valve calcium; Log – logarithm; AU - arbitrary units.

TABLE 4.2 Progression from baseline of aortic valve stenosis on echocardiography and computed tomography

Echocardiography	All patients (n = 134)	Atorvastatin (n = 65)	Placebo (n = 69)	Adjusted Difference: Atorvastatin – Placebo (95% CI)	P value
Aortic jet velocity (m/s/yr)	0.201 (0.208)	0.199 (0.210)	0.203 (0.208)	0.002 (-0.066, 0.070)	0.95
Peak gradient (mmHg/yr)	6.52 (7.24)	6.48 (7.43)	6.56 (7.10)	0.21 (-2.02, 2.45)	0.85
Aortic valve area (cm^2/yr)	-0.081 (0.107)	-0.079 (0.107)	-0.083 (0.107)	0.007 (-0.026, 0.040)	0.68
Computed Tomography	**All patients (n = 133)**	**Atorvastatin (n = 64)**	**Placebo (n = 69)**	**Adjusted Difference: Atorvastatin - Placebo (95% CI)**	**P value**
Absolute change AVC score (AU/yr)	1608 (1865)	1564 (1956)	1648 (1790)	85 (-554 to 723)	0.80
% Change in AVC score (%/yr)*	22.0 (4.6, 42.3)	22.3 (4.4, 43.3)	21.7 (4.6, 41.5)	0.998* (0.947, 1.050)	0.93

Variables stated as mean (SD).
***Analyses performed on log scale but presented as corresponding % change (± 1 SD) and ratio of adjusted post-treatment AVC scores on atorvastatin and placebo.**
CI - confidence interval; AVC - aortic valve calcium.

Figure 4.3 **Relationship between LDL cholesterol concentration and disease progression.**



LDL – low-density lipoprotein; AVC - aortic valve calcium.

TABLE 4.3 Secondary end-points

	Atorvastatin (n = 77)	Placebo (n = 78)	P value (Fisher's Exact Test)
Composite secondary end-point	13	21	0.19
Hospitalisation for severe aortic stenosis	3	5	0.73
Aortic valve replacement	11	19	0.17
Cardiovascular mortality	3	3	1.00
All cause mortality	3	5	0.73
All cardiac admissions	10	12	0.84

severe stenosis at baseline progressed more rapidly (p=0.04), but the study findings were consistent irrespective of baseline stenosis severity (Table 4.4). Likewise, length of follow-up did not influence outcome. In those followed up for >24 months, increase in aortic jet velocity was 0.21 ± 0.20 m/s per year in the atorvastatin group and 0.17 ± 0.14 m/s per year in the placebo group (Table 4.4).

4.4.4 ADVERSE EVENTS

High dose atorvastatin was well tolerated: the frequency of adverse events was similar in the two treatment groups. Discontinuation of the study drug occurred in 4 patients (5%) of the placebo group and 7 patients (9%) of the atorvastatin group (Fisher's exact test, p=0.52), predominantly as a result of gastrointestinal symptoms. Three patients in the atorvastatin group experienced an increase in creatine kinase to greater than five times the upper limit of normal without symptoms of myositis; one of whom was withdrawn at the request of the Data Monitoring Committee. There were no cases of rhabdomyolysis and no serious adverse events.

TABLE 4.4 Subgroup analyses of disease progression

Baseline severity of stenosis:		**Atorvastatin**	**Placebo**	
Mild to moderate (Baseline aortic jet velocity < 4 m/s)	**Baseline** (m/s)	3.12 (0.43) n = 58	3.18 (0.44) n = 61	**Interaction test: p = 0.57**
	Rate of change (m/s/yr)	**0.17 (0.21)** n = 49	**0.19 (0.20)** n = 55	
Severe (Baseline aortic jet velocity ≥ 4 m/s)	**Baseline** (m/s)	4.24 (0.21) n = 19	4.45 (0.26) n = 17	
	Rate of change (m/s/yr)	**0.27 (0.21)** n = 16	**0.27 (0.23)** n = 14	
Follow-up duration:		**Atorvastatin**	**Placebo**	
Follow-up ≤24 months (Median 23 months)	**Baseline** (m/s)	3.49 (0.69) n = 30	3.64 (0.67) n = 37	**Interaction test: p = 0.41**
	Rate of change (m/s/yr)	**0.19 (0.22)** n = 30	**0.23 (0.25)** n = 37	
Follow-up >24 months (Median 33 months)	**Baseline** (m/s)	3.31 (0.55) n = 35	3.28 (0.61) n = 32	
	Rate of change (m/s/yr)	**0.21 (0.20)** n = 35	**0.17 (0.14)** n = 32	

Mean (SD)

4.5 DISCUSSION

This is the first double-blind randomised controlled trial of lipid-lowering therapy in patients with calcific aortic stenosis. It has clearly demonstrated that whilst high dose atorvastatin more than halves serum LDL cholesterol concentrations, it does not halt the progression or induce regression of the valvular disease process. This has been demonstrated using two distinct measures of disease severity: aortic jet velocity determined by Doppler echocardiography and valvular calcification by helical CT. Moreover, there was no relationship between serum LDL cholesterol concentrations and the progression of aortic stenosis, nor was there a demonstrable effect of high dose atorvastatin on clinical end-points. Thus, irrespective of the method of assessing disease progression, we have consistently demonstrated the continued deterioration of aortic stenosis despite intensive reductions in serum cholesterol concentrations.

In this trial, there was a single co-ordinating centre with a consistent and reproducible approach to assessing the severity of aortic stenosis [Cowell *et al* 2003]. High dose atorvastatin therapy achieved the anticipated dramatic reduction in serum LDL cholesterol concentrations [Jones *et al* 1998], and disease progression was determined using two independent but complementary techniques. The trial employed a double-blind randomisation incorporating the minimisation technique to ensure no baseline inequalities between the treatment groups but, despite this rigorous methodology, we were unable to demonstrate a major impact on disease progression in these patients.

Several factors may have influenced our ability to detect an effect of statin therapy on the progression of aortic stenosis in this trial.

First, as a consequence of our inclusion criteria, we recruited some patients with advanced disease and an aortic jet velocity of ≥4 m/s and it could be argued that lipid-lowering therapy is unlikely to influence such an advanced stage of the disease. We therefore conducted a pre-specified subgroup analysis excluding patients with a baseline aortic jet velocity ≥4 m/s. Our findings were consistent irrespective of baseline stenosis severity and atorvastatin had no effect on disease progression even in the majority of individuals with mild to moderate stenosis. We excluded patients with aortic jet velocities below 2.5 m/s and we acknowledge that intervening at this earlier stage of the disease process may have been more beneficial. However, such patients do not commonly present to routine clinical practice.

Second, the length of treatment may have been inadequate and 2 years may not have been sufficient to influence the natural history of the disease. We assessed this possibility by determining if patients with longer-term follow-up demonstrated a treatment benefit. In patients maintained on nearly 3 years of treatment with intensive statin therapy, no trend towards a beneficial effect of atorvastatin was apparent. We therefore do not believe that the absence of an effect was due to an inadequate treatment period.

Finally, although this is the largest randomised controlled trial to date, our study was only designed to detect a substantial delay in disease progression and was not powered to assess meaningful effects on clinical end-points, such as valve replacement and cardiovascular death. Whilst we can exclude a treatment benefit of the magnitude previously reported in retrospective observational studies (aortic jet velocity, 0.30 m/s/yr [Rosenhek *et al* 2004] and valvular calcification, 30% per year [Pohle *et al* 2001; Shavelle *et al* 2002]), the 95% confidence intervals indicate that we may have missed a modest treatment benefit (a delay in disease progression of <0.07 m/s/yr, and <5%/yr respectively). Although such modest reductions are unlikely to be meaningful in the majority of older patients, a small decrease in disease progression may be clinically important in younger patients with mild disease who may progress over many years.

Given the strength of the data linking aortic stenosis with atherosclerosis and hypercholesterolemia, why have we have failed to halt the progression of calcific aortic stenosis? One potential explanation is that, whilst these features may drive the initiation of aortic stenosis, disease progression may be dependent upon other factors. The aortic valve is subject to continuous dynamic mechanical stress, and leaflet plasticity and structure can have an overriding influence, such as with a bicuspid valve. Moreover, in contrast to atherosclerosis, aortic stenosis is associated with a virtual absence of smooth muscle cell proliferation and lipid-laden macrophages [Otto *et al* 1994], and dominated by earlier and more extensive mineralisation. Decreasing the lipid pool and increasing the fibrous cap may be less relevant to the progression of aortic stenosis than it is for the

reduction in atherosclerotic plaque rupture with statin therapy in patients with coronary heart disease.

Statin therapy in patients with aortic stenosis may confer secondary preventative benefits that are independent of its effects on the valvular disease process because of the association between aortic stenosis and coronary artery disease. The current study was not powered to assess the benefits of lipid-lowering therapy on cardiovascular end-points such as non-fatal and fatal myocardial infarction. It remains a possibility that aortic stenosis and sclerosis [Otto *et al* 1999] may be important markers of occult vascular disease and thereby identify patients who would gain from the preventative benefits of statin therapy.

We conclude that intensive lipid-lowering therapy with atorvastatin 80 mg daily does not halt the progression, or induce the regression, of calcific aortic stenosis. Nevertheless, this trial does not exclude a modest reduction in the rate of disease progression or a significant reduction in major clinical end-points. Our study reinforces the need for a long-term large scale randomised controlled trial of intensive lipid-lowering therapy in patients with calcific aortic stenosis. In the meantime we do not recommend statin therapy for patients with calcific aortic stenosis in the absence of coexisting vascular disease.

CHAPTER 5

PROGRESSIVE CORONARY CALCIFICATION DESPITE INTENSIVE LIPID-LOWERING THERAPY:

A RANDOMISED CONTROLLED TRIAL

Based on

Houslay ES, **Cowell SJ**, Prescott RJ, Reid J, Burton J, Northridge DB, Boon NA, Newby DE, Scottish Aortic Stenosis and Lipid-Lowering Therapy, Impact on Regression Trial Investigators. Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial. *Heart* 2006;**92**(9):1207-12.

5.1 SUMMARY

Background Observational studies have suggested that statin therapy may induce regression of coronary artery calcification. In a substudy of a trial recruiting patients with calcific aortic stenosis, we evaluated the effect of intensive lipid-lowering therapy on coronary artery calcification.

Methods In a double-blind randomised controlled trial, 102 patients with calcific aortic stenosis and coronary artery calcification were randomised using the minimisation technique to atorvastatin 80 mg daily or matched placebo. Coronary artery calcification was assessed annually by helical CT.

Results Forty-eight patients were randomised to atorvastatin and 54 to placebo with a median follow-up of 24 months (interquartile range 24-30). Baseline characteristics and coronary artery calcium scores were similar in both groups. Atorvastatin therapy reduced serum low-density lipoprotein cholesterol (-53%; $p<0.001$) and CRP (-49%; $p<0.001$) concentrations whilst there was no change with placebo (-7% and +17%; $p>0.95$ for both). The rate of change in coronary artery calcification was 26% per year (0.234 (standard error (SE) 0.037) log AU/yr; n=39) in the atorvastatin group and 18% per year (0.167 (SE 0.034) log AU/yr; n=49) in the placebo group: geometric mean difference of +7% per year (95% CI -3% to +18%; p=0.18). There was no correlation between serum low-density lipoprotein concentrations and the rate of progression of coronary calcification (r=0.05, p=0.62).

Conclusion In contrast to previous observational studies, this randomised controlled trial has shown that, despite reducing systemic inflammation and halving serum

low-density lipoprotein cholesterol concentrations, statin therapy does not have a major effect on the rate of progression of coronary artery calcification.

5.2 INTRODUCTION

Coronary artery calcification is an independent risk factor for coronary heart disease with even low coronary calcium scores doubling the risk of coronary events [Pletcher *et al* 2004]. The relative risk associated with coronary calcification is greater than that associated with established factors such as smoking, hypertension and diabetes mellitus. Progression of coronary artery calcification is associated with a higher incidence of coronary events even in those people who are asymptomatic at the time of initial scanning [Raggi *et al* 2003] Thus, the presence of coronary artery calcification is not only indicative of atheromatous plaque disease, but its progression may correspond with cardiovascular event rates.

Statin therapy has a proven role in the primary [Shepherd *et al* 1995; Downs *et al* 1998] and secondary prevention [The Scandinavian Simvastatin Survival Study (4S) 1994; Lewis *et al* 1998; The LIPID Study Group 1998; The Heart Protection Study Collaborative Group 2002] of cardiovascular disease with incremental benefits seen with more intensive reductions in serum cholesterol concentrations [The Heart Protection Study Collaborative Group 2002]. Previous studies [Callister *et al* 1998; Achenbach *et al* 2002] have reported that statins can halt the progression and may even induce regression of coronary artery calcification. Indeed, the rate of progression of coronary

artery calcification correlates with the average serum LDL cholesterol concentration [Callister *et al* 1998]. This has led to the use of CT to monitor disease progression and response to treatment, particularly statin therapy. However, two recent trials have failed to demonstrate a benefit of statin therapy on the progression of coronary artery calcification in asymptomatic individuals [Arad *et al* 2005; Raggi *et al* 2005].

The Scottish Aortic Stenosis Lipid lowering Therapy, Impact on REgression trial was a prospective double-blind randomised controlled study of intensive lipid-lowering therapy in patients with calcific aortic stenosis [Cowell *et al* 2005]. As part of this trial, aortic valve and coronary artery calcium scores are measured using helical CT. The aim of this substudy was to assess the effect of atorvastatin 80 mg daily on the rate of progression of coronary artery calcification in patients with calcific aortic stenosis.

5.3 METHODS

5.3.1 PATIENT POPULATION

Patients aged >18 years, with calcific aortic stenosis (grade 1-3 calcification on echocardiography [Rosenhek *et al* 2000]) and a peak post-valve velocity of ≥2.5 m/s were recruited from eight hospital centres across the South East of Scotland. Exclusion criteria are outlined in Chapter 2. For the purposes of the substudy, we also excluded patients who had no coronary artery calcification on CT. The study was conducted with the approval of all regional research ethics committees and in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject.

5.3.2. STUDY PROTOCOL

Between March 2001 and April 2002, the blinded study co-ordinator randomised eligible patients by the minimisation technique [Treasure and MacRae 1998] using a dedicated locked computer program (Edinburgh University) which incorporated eight baseline variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, peak aortic jet velocity and aortic calcium score. Patients were assigned either to atorvastatin 80 mg daily or matched placebo (Pfizer Ltd., Tadworth, UK) as a single daily dose using numbered containers.

Patients were assessed at baseline, 2 months, 6 months and every 6 months thereafter for a minimum of 2 years. Clinical evaluation included assessment of functional status, adverse events and biochemical blood analysis. Serum highly sensitive C-reactive protein (hsCRP) concentrations were determined using a highly sensitive immunonephelometric method (Dade Behring Ltd, Milton Keynes, UK) as previously described [Carr *et al* 2000]. All patients underwent CT within the month before randomisation to study therapy and at each annual visit. Randomised patients who were subsequently commenced on open label statin therapy by their attending physician were immediately scanned and withdrawn from further observation.

5.3.3 COMPUTED TOMOGRAPHY

Computed tomography was performed by a single-blinded operator using a double-helix scanner (Twin II Flash; Philips Medical Systems (UK) Ltd, Stevenage, UK) and

calibrated against a standard phantom. Images were acquired in 2.7 mm slices (with a 0.75 s full 360° scan mode) through the region of the coronary arteries with a pitch of 0.7 and an increment of 1.3 mm during held inspiration. Exposure factors were 120 kV at 270 mAs and the scan angle was 360°. Off-line analyses were conducted using an automated, computerised software program (Picker Cardiac Scoring). This employs an Agatston scoring method [Agatston *et al* 1990], producing sensitivity and specificity comparable to electron beam CT [Carr *et al* 2000]. Scans were scored using both the Agatston (130 HU threshold) and the modified Agatston (90 HU threshold) methods [Shemesh *et al* 1995]. The former has been shown to reduce interobserver and interscan variation compared to the threshold of 90 HU [Goldin *et al* 2001]. To assess the reproducibility of the method, repeated baseline CT scans were performed within 4 weeks of each other in an unselected random sample of 16 patients.

5.3.4. DATA ANALYSIS AND STATISTICS

Coronary artery calcium scores are expressed in AU using the 130 HU threshold. The calcium scores and hsCRP concentrations were not normally distributed and data are presented as median with interquartile ranges or mean and standard deviation following logarithmic transformation. The primary end-point, the rate of change of coronary calcium scores, was analysed using random coefficient models [Bland and Altman 1986; Cowell *et* al 2005] after logarithmic transformation of the scores. In summarising the data, the change in coronary artery calcium scores was calculated by dividing the change between the baseline and final scores by the duration of follow-up. Rate of change in coronary calcium score is expressed as percentage change per year or as absolute change

in the logarithm of the coronary artery calcium score. Reproducibility was assessed using the method of Bland and Altman [Bland and Altman 1986]. As well as tests of significance, 95% confidence intervals are reported as appropriate. Statistical significance was taken as a two-sided p value <0.05.

5.4 RESULTS

Of 155 patients recruited into the SALTIRE trial, 102 had coronary calcification at baseline (Figure 5.1) of whom 88 had at least two scans. Coronary calcification predominated in the left anterior descending coronary artery (100% of patients) although it was also present in the circumflex (33%) and right (27%) coronary arteries. Baseline characteristics and coronary artery calcium scores were well matched in both treatment groups (Table 5.1) in the 88 evaluable subjects.

5.4.1 REPRODUCIBILITY

The reproducibility of the LAD coronary score and of the total coronary score was examined using the approach of Bland and Altman [Bland and Altman 1986]. Without transformation, the difference between replicate observations tended to increase with the magnitude of the measurement. After logarithmic transformation, higher values showed stable differences, but differences were higher at the lowest scores. Overall, the

Figure 5.1 CONSORT flow diagram of patients recruited into the trial and substudy. (ITT - intention-to-treat; CT - computed tomography).

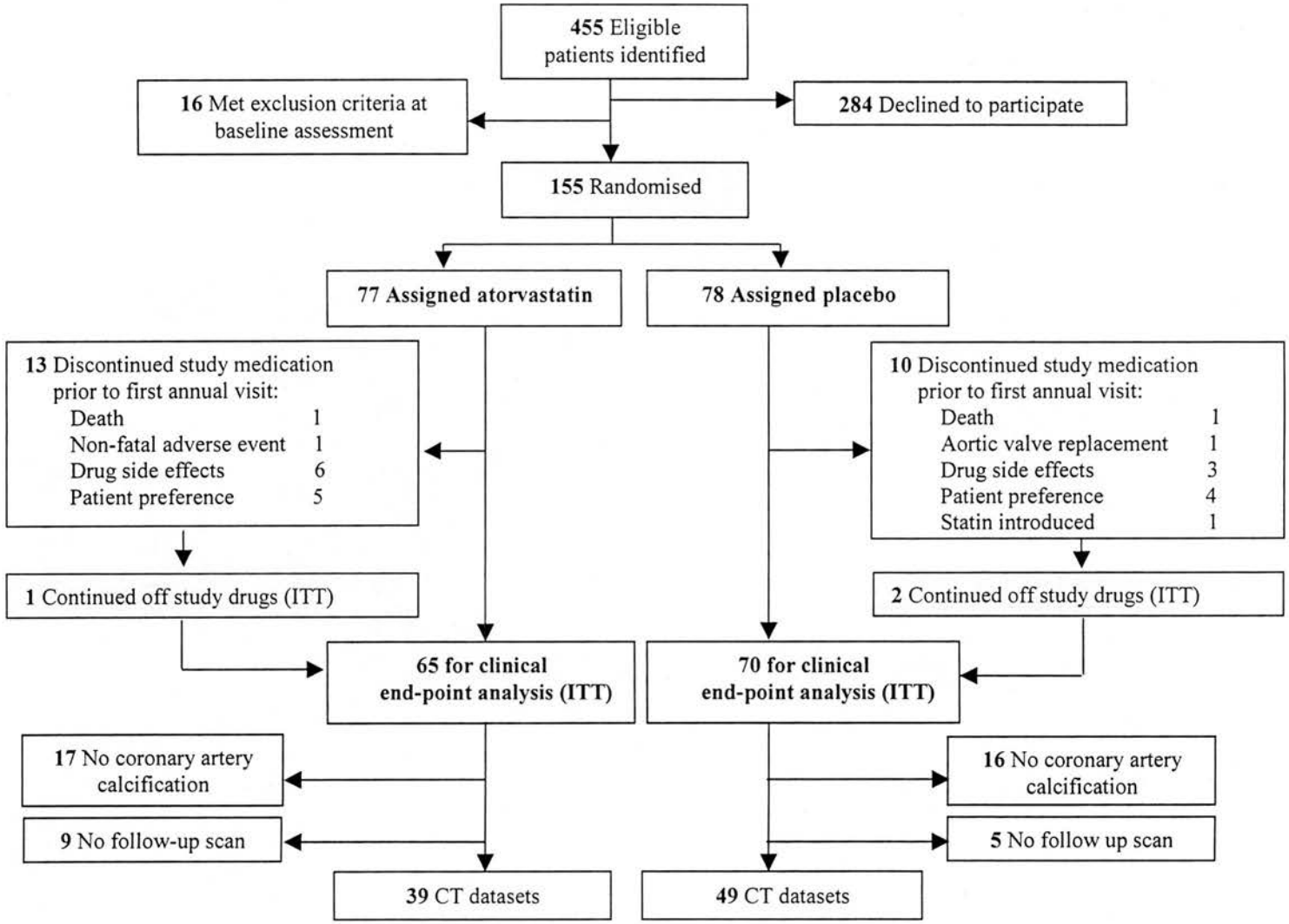


TABLE 5.1 Baseline subject characteristics

	Atorvastatin (n = 39)	**Placebo** (n = 49)
Age (years)	70 (8)	70 (9)
Sex (% male)	74	78
Body mass index	29 (5)	28 (5)
Cardiovascular Risk Factors		
Hypertension	22	28
Hyperlipidaemia	3	2
Diabetes mellitus	0	2
Current smoker	5	10
Cardiovascular Disease		
Coronary heart disease	7	13
Cerebrovascular disease	5	7
Peripheral vascular disease	3	7
Drug History		
Aspirin	17	26
ACE inhibitor	7	8
Beta-blocker	11	15
Warfarin	4	8
Blood Pressure (mmHg)		
Systolic blood pressure	143 (18)	140 (19)
Diastolic blood pressure	82 (11)	78 (11)
Lipid Profile		
Total cholesterol (mmol/L)	5.7 (0.9)	5.5 (0.9)
LDL cholesterol (mmol/L)	3.6 (0.8)	3.4 (0.7)
HDL cholesterol (mmol/L)	1.5 (0.4)	1.5 (0.4)
Cholesterol: HDL ratio	4.2 (1.2)	4.0 (1.0)
Triglycerides (mmol/L)	1.5 (0.8)	1.4 (0.7)
Coronary calcification score (AU)		
Left anterior descending	112 (40– 285)	207 (76 – 461)
Circumflex	0 (0 – 9)	0 (0 – 4)
Right	0 (0-29)	0 (0 – 0)
Total coronary score	195 (57 – 448)	235 (83 – 526)
Log total coronary score (LogAU)	2.16 (0.68)	2.30 (0.65)

Continuous variables stated as mean (SD) or median (interquartile range).
Categorical variables stated as per cent.
ACE - angiotensin-converting enzyme; LDL - low-density lipoprotein; HDL - high-density lipoprotein; Log - logarithm.

differences on the log scale correspond to a coefficient of variation of 28% for both variables, but when restricted to the ten pairs with a geometric mean score above 100, the coefficient of variation was 10% for both variables.

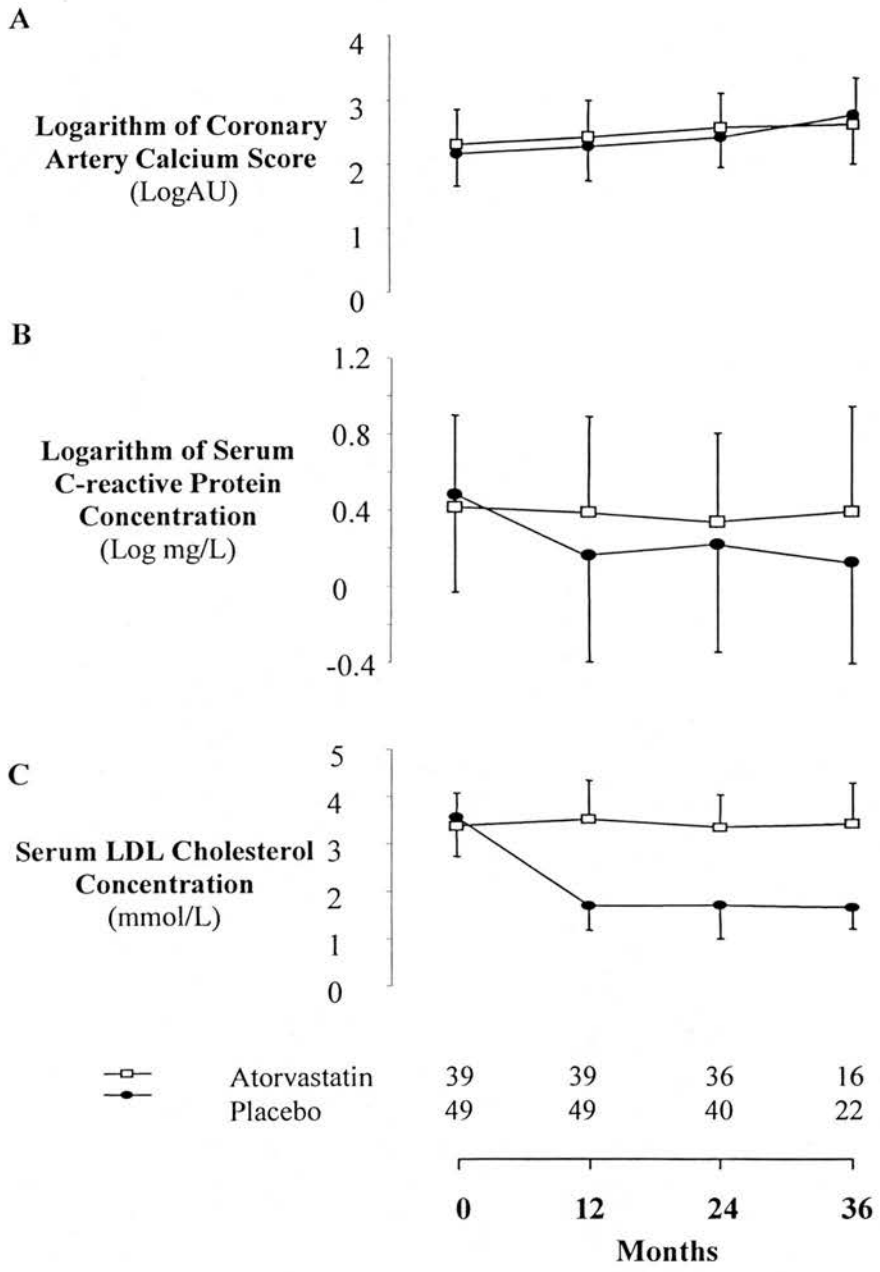
5.4.2 Effect of atorvastatin treatment

Patients were followed-up for a median of 24 months (interquartile range 24-30). Atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations (53 (SD 19) %; $p<0.001$), whilst placebo had no effect (Figure 5.2). This reduction in serum LDL cholesterol concentrations was associated with a marked decrease in serum CRP concentrations from 1.95 (interquartile range 1.15-4.86) to 1.00 (0.49-2.31) mg/L (Wilcoxon Signed Rank, $p<0.001$; Figure 5.2). Atorvastatin was well tolerated with discontinuation of study medication in 2 patients on placebo and 5 patients on atorvastatin, predominantly as a result of gastrointestinal upset. One patient on atorvastatin had an increase in creatine kinase of >5 times the upper limit of normal without symptoms of myositis, and was withdrawn at the request of the Data Monitoring Committee. There were no cases of rhabdomyolysis.

5.4.3 Coronary Artery calcium score

Atorvastatin did not affect the rate of progression of coronary artery calcium score (Figure 5.2). Similar results were obtained when employing the 90 HU threshold (42 (SD 73) %/yr in the atorvastatin group and 29 (SD 37) %/yr in the placebo group; $p=0.24$). Serum LDL cholesterol concentrations did not correlate with the rate of progression of coronary artery calcification ($r=0.05$, $p=0.62$).

Figure 5.2 **Progression of (A) coronary artery calcification, (B) serum C-reactive protein concentrations (p <0.001, atorvastatin *versus* placebo), and (C) serum low-density lipoprotein (LDL) cholesterol concentrations (p s<0.001, atorvastatin *versus* placebo) in patients treated with atorvastatin 80 mg daily (solid circles) or matched placebo (open squares).**

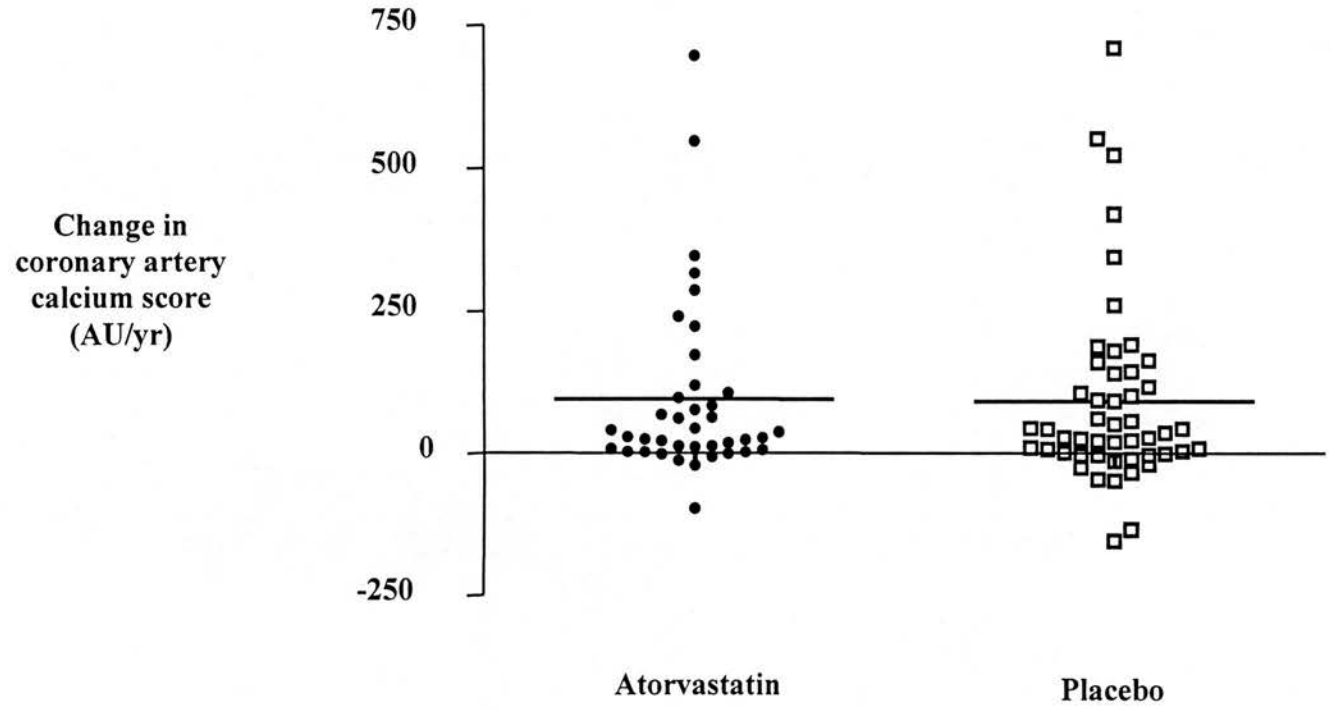


LDL - low-density lipoprotein; Log - logarithm; AU - arbitrary units.

The primary analysis of the rates of change of coronary artery calcium scores was conducted on the logarithms of the scores using random coefficients models [Brown and Prescott 1999]. This showed no difference between the average rates of change in the two treatment arms (p=0.18). The mean coronary calcium score increased by 0.234 (SE 0.037) log AU per year in the atorvastatin group and 0.167 (SE 0.034) log AU per year in the placebo group. These figures correspond to a 26% per year increase in the atorvastatin group and 18% per year in the placebo group. The geometric mean (adjusted for baseline) is 7% higher at one year on atorvastatin compared to placebo, with 95% confidence limits ranging from 3% lower to 18% higher. The observed annual changes in coronary calcium scores, calculated from the first to the last visit, are summarised in Figure 5.3.

As anticipated in such a small clinical trial, there were no significant differences in all cause mortality, cardiovascular mortality or cardiovascular hospitalisation between the two groups.

Figure 5.3 Absolute rate of change in coronary calcium score expressed in AU per year for patients treated with atorvastatin 80 mg (solid circles) or matched placebo (open squares).



AU - arbitrary units.

5.5 DISCUSSION

We have confirmed that, despite marked reductions in serum LDL cholesterol and CRP concentrations, atorvastatin 80 mg daily did not halt the progression, or induce regression, of coronary artery calcification in patients with calcific aortic stenosis. Consistent with recent trials of asymptomatic individuals [Arad *et al* 2005; Raggi *et al* 2005], our findings are in marked contrast to previous observational studies and suggest that the potential beneficial effects of statin therapy on coronary artery calcification have been over estimated.

Previous observational and non-randomised prospective studies [Callister *et al* 1998; Achenbach *et al* 2002] have suggested that reductions in serum LDL cholesterol concentrations decrease the progression of coronary calcification. However, not all observational studies have demonstrated consistent findings. In the largest observational study of 182 patients, Hecht and colleagues recently found no difference in the progression of coronary calcium scores in patients who were maintained on lipid-lowering therapy and achieved significant reductions in serum LDL cholesterol concentrations [Hecht and Harman 2003]. Observational data may be misleading and prospective randomised controlled trials are necessary to confirm or to refute these interesting preliminary observations. The recent BELLES trial [Raggi *et al* 2005] found no differential effect of pravastatin (40 mg daily) and atorvstatin (80 mg daily) on the progression of coronary artery calcification in 615 hyperlipidaemic post-menopausal women. However, study follow-up was brief (1 year) and there was no placebo control

group. The St Francis Heart Study [Arad *et al* 2005] randomised 1,005 asymptomatic middle-aged men and women with high coronary artery calcium scores to combination atorvastatin 20 mg, vitamin C 1 g and vitamin E (alpha tocopherol) 1,000 units daily or matching placebos. After 4.3 years of follow-up, there were no differences in the rate of progression of coronary artery calcification.

We have conducted a double-blind randomised controlled trial using helical CT in patients with aortic stenosis. Minimisation technique ensured good matching of the baseline characteristics of the patient population and reproducibility studies confirmed the validity of our repeated assessments. Although documenting very similar rates of progression of coronary calcification to previous studies [Callister *et al* 1998; Achenbach *et al* 2002; Hecht and Harman 2003], we have not observed a reduction in coronary calcification with intensive lipid-lowering therapy despite more than halving serum LDL cholesterol concentrations.

Statin therapy has been extremely successful in the primary and secondary prevention of cardiovascular disease. Why then have we and others not observed a beneficial effect of statin therapy on coronary artery calcification? Unstable atherosclerotic plaques have a large lipid-rich core, a preponderance of macrophages and foam cells, and a thin fibrous cap containing few smooth muscle cells [Davies 1997]. It has been suggested that calcified lesions may be relatively more stable [Mintz *et al* 1995], indicating a possible protective role of calcification in coronary plaques. Statin therapy produces many of its beneficial effects through plaque stabilisation. In both primate [Stary 2001] and swine

[Daoud *et al* 1981] models, anti-atherosclerotic interventions are associated with an increase in vascular fibrous tissue and calcification. This calcium deposition continues during the initial phase of plaque regression due to the death of foam cells and an increase in necrotic tissue. Thus vascular calcification may play a role in the initial stabilisation of atherosclerotic plaques. This is consistent with our findings and would account for the lack of effect on the progression of coronary artery calcification despite a reduction in serum CRP concentrations.

After the initial stabilisation of the atherosclerotic plaque, it would be anticipated that subsequent progression of coronary calcification would be inhibited. The present study was brief, and follow-up was only continued for a median of 2 years. It would be important to extend our observations to 5 or more years to assess properly the impact of statin therapy on the long-term progression of coronary artery calcification. However, it should be acknowledged that the clinical benefits of statin therapy are apparent within the first few years [Lewis *et al* 1998; The LIPID Study Group 1998; The Heart Protection Study Collaborative Group 2002], and in some cases the first few months [Schwartz *et al* 1998], of therapy. Moreover, the St Francis Heart Study demonstrated no beneficial effects despite 4.3 years of follow-up [Arad *et al* 2005].

On the basis of previous non-randomised studies [Achenbach *et al* 2002], the practice of performing serial CT scans to monitor disease progression and the response to treatment has become widespread, especially in North America. Our data, and that of the St Francis Heart Study [Arad *et al* 2005] and the BELLES study [Raggi *et al* 2005],

indicate that repeated scanning to assess response to statin therapy is not justified. Indeed, the radiation dose incurred for such serial scans poses potential health risks, particularly when employing multidetector CT scanners.

5.5.1 Study limitations

There are several factors that should be taken into account when considering the results of our study. This was a substudy of the SALTIRE trial [Cowell *et al* 2005] that recruited only patients with calcific aortic stenosis. However, our findings are consistent with two recent randomised controlled trials in asymptomatic younger individuals without valvular heart disease [Arad *et al* 2005; Raggi *et al* 2005]. Our study therefore suggests that failure of statins to restrict the progression of coronary artery calcification can be extended to include patients with valvular heart disease as well as more elderly populations. Moreover, our findings suggest that lack of benefit seen in the St Francis Heart Study is not attributable to the modifying effects of antioxidant vitamins [Arad *et al* 2005].

When compared with electron beam CT, the accuracy of helical CT in detecting coronary artery calcification has been questioned [Carr *et al* 2000; Qanadli *et al* 2001]. Technological advances have also meant that double-helical scanners have now been overtaken by 64 or higher slice scanners. At trial inception, the double-helix scanner was "state-of-the-art" and it would have been inappropriate to replace the scanner during the conduct of the trial. Moreover, our approach has been previously validated [Bland and Altman 1986] and we have demonstrated good reproducibility of coronary artery

calcification scores in patients with scores of greater than 100 AU. We do not believe the absence of a major beneficial effect on coronary artery calcification is attributable to our methodology. We acknowledge the fact that our population size is modest; however, the 95% confidence intervals are able to exclude a relative reduction in progression of coronary artery calcification of >3% per year. We therefore suggest that if lipid-lowering therapy does reduce the progression of coronary artery calcification then the effect is rather small.

Controversy exists over the method of quantification of coronary artery calcification. The Agatston method is traditionally employed but this may overestimate the coronary calcium score in newer generation scanners with reduced slice thickness due to partial voluming. More recent methods include the volume [Callister *et al* 1998] and the coronary calcium mass [Hong *et al* 2002] scores, although neither are superior to the Agatston score in terms of reproducibility from consecutive scans in an individual patient [Rumberger and Kaufman 2003].

5.6 CONCLUSION

We conclude that intensive lipid-lowering therapy does not halt the progression, or induce regression, of coronary artery calcification. Although coronary artery calcium scores correlate well with the presence of atherosclerosis and predict future coronary risk, our findings confirm that there is currently no role for monitoring progression of coronary artery calcification in order to assess the response to lipid-lowering therapy.

CHAPTER 6

PREDICTORS OF DISEASE PROGRESSION AND CLINICAL OUTCOME IN PATIENTS WITH CALCIFIC AORTIC STENOSIS

6.1 SUMMARY

Background Calcific aortic stenosis results from an active inflammatory process closely resembling atherosclerosis. We hypothesised that risk factors for atherosclerosis would predict disease progression and clinical outcome of patients with calcific aortic stenosis.

Methods Patients (n=155; 68 ± 11 yrs) with calcific aortic stenosis participating in the SALTIRE trial (randomised comparison of atorvastatin 80 mg daily or matched placebo) were followed-up for 26 ± 7 months. Severity of aortic valve stenosis and calcification was assessed longitudinally using echocardiography and helical CT respectively.

Results Aortic jet velocity progressed by 0.20 ± 0.21 m/s per year and calcification by 29 ± 30% per year and was unaffected by atorvastatin therapy. Disease progression was predicted by age ($p<0.01$), sex ($p=0.02$), height ($p=0.03$), hypertension ($p=0.03$), serum BNP concentration ($p=0.002$), and baseline valve disease severity as determined by both aortic jet velocity ($p<0.001$) and valvular calcification ($p<0.001$). Clinical outcome was predicted by baseline and rate of progression of aortic stenosis severity ($p<0.002$) and serum BNP concentrations ($p\leq0.02$). Clinical and biochemical markers of atherosclerosis, including serum CRP and cholesterol concentrations, did not predict disease progression or clinical outcome.

Conclusions The major predictors of disease progression and clinical outcome in patients with aortic stenosis are measures of disease severity; namely aortic jet velocity, aortic valve calcification and serum BNP concentration. With the exception

of hypertension the presence of clinical atherosclerotic risk factors do not influence the rate of progression.

6.2 INTRODUCTION

Aortic stenosis is the commonest adult heart valve condition seen in the western world affecting 2% of individuals over the age of 65 [Cowell *et al* 2004]. Thickening and calcification of the valve leaflets progresses slowly over many years. The outlook for patients with asymptomatic aortic stenosis is generally good, but although prognosis is similar to life table estimates for age and sex matched controls [Pellikka *et al* 1990], there is an increased risk of unrelated cardiovascular events [Iivanainen *et al* 1996; Otto *et al* 1999; Rosenhek *et al* 2004]. In patients with severe stenosis, the onset of symptoms dramatically changes the outlook with 2-year survival rates falling to 50% [Otto *et al* 1999; Rosenhek *et al* 2000]. At the present time, the only treatment option of prognostic benefit is aortic valve replacement.

Calcific aortic stenosis has for many decades been attributed to age-associated "wear and tear", but a third of individuals over the age of 80 [Lindroos *et al* 1993] have no evidence of aortic valve calcification or stenosis. Moreover, histological examination of stenotic aortic valves reveals features of chronic inflammation that resemble those seen in atherosclerosis, and are distinct from those changes occurring with ageing alone [Olsson *et al* 1994; Otto *et al* 1994]. In addition, calcific aortic stenosis is associated with coronary artery disease and its risk factors including age, male sex,

smoking, hypertension, diabetes mellitus, coronary artery disease and hyperlipidaemia [Cowell *et al* 2004].

Disease progression in aortic stenosis is variable and unpredictable. Both disease progression and clinical outcome have been linked to many of the risk factors for aortic stenosis, but much of the evidence is conflicting and based on retrospective studies [Peter *et al* 1993; Bahler *et al* 1999; Palta *et al* 2000; Ngo *et al* 2001; Wongpraparut *et al* 2002]. The most consistent and strongest predictors of disease progression appear to be severity of stenosis [Otto *et al* 1997; Bahler *et al* 1999] and the degree of valvular calcification [Davies *et al* 1991; Bahler *et al* 1999; Rosenhek *et al* 2004a]. The more severe the stenosis and the more heavily calcified the valve, the faster the rate of disease progression. Clinical outcome is influenced by the rate of disease progression as well as the degree of valvular calcification, with nearly 80% of patients with moderate to severe calcification who progress rapidly (>0.3 m/s/yr) either dying or undergoing AVR within 2 years [Rosenhek *et al* 2000].

Using the SALTIRE trial population [Cowell *et al* 2005], we wished to identify prospectively the clinical and biochemical variables associated with disease progression and clinical outcome in patients with calcific aortic stenosis. We assessed clinical risk factors as well as other novel predictors of cardiovascular risk including inflammatory, vascular and cardiac markers. In particular, we hoped to identify modifiable risk factors, with the potential of delaying or avoiding the need for AVR. Identification of markers capable of predicting risk might also facilitate the appropriate timing of aortic valve surgery.

6.3 METHODS

6.3.1 PATIENT POPULATION

All 155 patients randomised to the SALTIRE trial (a randomised controlled trial assessing the effects of atorvastatin therapy on the progression of aortic valve stenosis and calcification) [Cowell *et al* 2005] were included in this substudy. Patients aged >18 years with calcific aortic stenosis, an aortic jet velocity of ≥2.5 m/s, and grade 1-3 calcification of the aortic valve on echocardiography were included. Exclusion criteria are detailed in Chapter 2. All patients had asymptomatic aortic stenosis at entry into the study, and were randomised to receive either atorvastatin 80 mg daily or matched placebo. The investigation conformed to the Declaration of Helsinki, and was approved by all regional ethics committees. All patients gave written informed consent.

6.3.2 STUDY PROTOCOL

Patients were assessed at baseline, at 2 and 6 months, and 6 monthly thereafter for a minimum of 2 years. Baseline characteristics evaluated included demographics, cardiovascular risk factors, functional status (NYHA classification), blood pressure, arterial stiffness (pulse wave analysis), and biochemical variables including lipid profile, renal function, BNP, CRP and calcium concentrations. Subsequent evaluation comprised assessment of biochemical blood analysis, arterial stiffness and adverse clinical events. Echocardiography and CT were performed at baseline, at each annual visit or prior to withdrawal from the study.

6.3.3 ECHOCARDIOGRAPHY

Assessment of valvular stenosis was determined by a single dedicated research ultrasonographer. Patients were studied using a 3-MHz transducer for M-mode, and two-dimensional imaging with integral pulsed, continuous wave and tissue Doppler. All measurements were determined on-line, averaged from three cardiac cycles (five cycles if in atrial fibrillation), and recorded onto Super-VHS video and optical disk using a standardised proforma. Peak and mean aortic valve gradients were calculated using the Bernoulli equation, and AVA using the continuity equation.

6.3.4 COMPUTED TOMOGRAPHY

Computed tomography was performed by a single operator using a double-helix scanner (Twin II Flash; Philips Medical Systems Ltd, Stevenage, UK) and calibrated against a standard phantom. The region of the aortic valve was imaged with a spiral acquisition using 2.7 mm slices, with a pitch of 0.7 and an increment of 1.4 mm during held inspiration. All images were analysed by a single operator using automated computerised software (Picker Cardiac Scoring). This employs a modified Agatston scoring method [Shemesh *et al* 1995] that uses a threshold of 90 HU to compensate for non-gated imaging.

Reproducibility of echocardiography and CT assessments was determined in two subsets of 20 patients as described in Chapter 3. Coefficients of reproducibility for aortic jet velocity and AVC score were 0.32 m/s and 0.07 pAU respectively.

6.3.5 BIOCHEMICAL VARIABLES

Fasting venous blood samples were taken annually. Samples for serum electrolytes, lipid profile and calcium concentrations were sent to the regional clinical laboratory for immediate analysis. Samples for estimation of serum BNP and CRP concentrations were centrifuged at 4°C and stored at -80° C for later analysis. N-terminal pro-BNP was measured using a chemiluminescent immunoassay (Roche Diagnostics Ltd, Lewes, U.K.) on an Elecsys 2010 analyser. Serum highly sensitive CRP concentrations were determined using a highly sensitive immunonephelometric method (Dade Behring Ltd, Milton Keynes, UK).

6.3.6 PULSE WAVE ANALYSIS

Pulse wave analysis was performed at baseline and 6 monthly intervals thereafter. Patients were rested supine for 15 minutes prior to study. Radial pulse wave analysis was performed using a high-fidelity applanation tonometer (Sphygmocor BPAS; PWV Medical, Sydney, Australia). After acquiring a series of consecutive waveforms, an averaged peripheral waveform was acquired and a generalised transfer function was used to generate a central aortic pressure waveform from which the pulse pressure, augmentation pressure and augmentation index were determined. Two measurements of augmentation within 5 mmHg of each other were recorded on each occasion. Patients with atrial fibrillation were excluded, and recordings with poor quality waveforms were discarded: determined by visual inspection (SJC) with minimum requirements in pulse height of >100 mmHg, diastolic variation of <5% and pulse height variation of <5%. Data on 105 patients were available at baseline, of these 20 patients had poor quality recordings and 9 patients were in atrial fibrillation, leaving a total of 84 patients for analysis.

6.3.7 CLINICAL FOLLOW-UP

The following clinical end-points were recorded throughout the study; cardiovascular and all cause mortality, AVR (whether for severe symptomatic stenosis or not), and the development of symptoms attributable to severe aortic stenosis (confirmed by the patient's treating physician).

6.3.8 DATA ANALYSIS AND STATISTICS

Disease progression was determined by measuring the annual rate of change in aortic jet velocity on echocardiography, and the change in aortic valve calcification on CT by dividing the difference between baseline and final scans by the duration of follow-up. The CT, BNP and CRP data were log transformed prior to analysis as the data were not normally distributed. Predictors of progression were determined using regression analysis for continuous variables, and Chi-squared tests for categorical variables. Predictors of outcome were determined using Chi-squared tests for categorical variables, *t*-tests for continuous variables. Statistical significance was taken as two-sided $p<0.05$.

6.4 RESULTS

One hundred and fifty-five patients (mean age 68 years, 70% male) with calcific aortic stenosis were randomised to the SALTIRE trial [Cowell *et al* 2005] and were followed-up for a median of 25 months (range 7-36).

At baseline (Table 6.1) mean aortic jet velocity was 3.42 ± 0.64 m/s (range 2.5-5.0), and increased by 0.20 ± 0.21 m/s per year (Table 6.2). Median AVC score at baseline was 5920 AU (interquartile range 2485-14231 AU), and increased by 29 ± 30% per year. A number of patients had risk factors for cardiovascular disease (Table 6.1) and at baseline the mean total cholesterol was 5.7 mmol/L. As previously reported (Chapter 4) [Cowell *et al*, 2005], there was no difference between the treatment groups despite a 53% reduction in serum LDL cholesterol concentrations ($p<0.001$) in the atorvastatin group. Given the absence of a treatment effect, all patients have been included in the subsequent analyses.

6.4.1 Disease progression

The results of univariate analyses are presented in Tables 6.3 and 6.4. In keeping with previous observation studies [Bahler *et al* 1999], we have now demonstrated prospectively that progression of aortic jet velocity is strongly correlated with baseline aortic jet velocity ($p<0.001$; Table 6.3), and furthermore is correlated with baseline and progressive increases in the absolute AVC score ($p=0.004$ and $p=0.002$ respectively). Annual progression in aortic jet velocity was also strongly associated with age ($p=0.006$), baseline log BNP ($p=0.003$) and the rate of change in log BNP per year ($p=0.002$), but only weakly with height ($p=0.03$), male sex ($p=0.02$) and the presence of hypertension ($p=0.03$) (Tables 6.3 and 6.4).

TABLE 6.1 Baseline Characteristics

	All patients n = 155
Demographics	
Age (years)	67.8 (10.6)
Male Sex	108 (69.7%)
Cardiovascular Risk Factors	
Hypertension	79(50.6%)
Hypercholesterolaemia	10 (6.5%)
Diabetes Mellitus	5 (3.2%)
Current smoker	33 (21.3%)
Cardiovascular Disease	
Coronary artery disease	30 (19.4%)
Cerebrovascular disease	16 (10.3%)
Peripheral vascular disease	14 (9.0%)
Drug History	
Aspirin	64 (41.0%)
Warfarin	15 (9.6%)
Beta-blocker	37(23.7%)
ACE inhibitor	20 (12.8%)
NYHA Class	
Class I	12 (8%)
Class II	125 (80.6%)
Class III	18 (11.6%)
Class IV	0
Physical Examination	
Height (cm)	168.5 (8.3)
Weight (Kg)	79.3 (14.8)
Heart rate (beats/min)	67 (11.6)
Systolic blood pressure (mmHg)	144 (19.8)
Diastolic blood pressure (mmHg)	81.8 (11.0)
Electrocardiography	
Sinus rhythm	144 (93%)
Atrial fibrillation	10 (6.5%)
Echocardiography	
Bicuspid valve	5 (3.2%)
Tricuspid valve	150 (96.8%)

\ continued

TABLE 6.1 Baseline Characteristics continued /

Echocardiography	**n = 155**
Peak aortic jet velocity (m/s)	3.42 (0.64)
Peak gradient (mmHg)	48.6 (18.4)
Aortic valve area (cm^2)	1.02 (0.4)
LV mass (g)	354 (110)
LV mass index (g/m^2)	176 (55)
Fractional shortening (%)	40 (8.4)
Computerised Tomography	**n = 155**
AV calcium score (AU) †	5920 (2485-14231)
Mean Log AV calcium score (LogAU)	3.67 (0.53)
Pulse Wave Analysis	**n = 110**
Pulse pressure, PP (mmHg)	61 (17)
Augmentation pressure, AG (mmHg)	16 (9)
Augmentation index AG/PP (%)	31 (12)
Augmentation index P2/P1 (%)	149 (29)
Serum Biochemistry	**n = 155**
Total cholesterol (mmol/L)	5.7 (1.0)
HDL cholesterol (mmol/L)	1.5 (0.4)
HDL:Total cholesterol ratio	4.1 (1.2)
Triglycerides (mmol/L)	1.5 (0.7)
LDL cholesterol (mmol/L)	3.5 (0.8)
Urea (mmol/L)	6.5 (5.0)
Creatinine (μmol/L)	92 (21.4)
Glucose (mmol/L)	5.3 (1.2)
Calcium (mmol/L)	2.32 (0.10)
Brain Natriuretic Peptide (pg/ml)	**n = 134**
Mean (SD)	465 (633)
Median (Range)	200 (14-3640)
Log BNP (Log pg/ml)	2.37 (0.52)
C-Reactive Protein (mg/L)	**n = 135**
Mean (SD)	4.3 (6.2)
Median (Range)	2.35 (0.16-38.0)
Log CRP (Log mg/L)	0.39 (0.5)

Categorical variables stated as number, n (%). Continuous variables stated as mean (standard deviation). † Median (Range).
ACE - angiotensin-converting enzyme; NYHA - New York Heart Association; LV - left ventricular; AV - aortic valve; Log - logarithm; HDL - high-density lipoprotein; LDL - low - density lipoprotein; BNP - brain natriuretic peptide.

TABLE 6.2 Progression of aortic valve stenosis and calcification

Progression of stenosis (Echocardiography)	**n = 134**
Peak velocity (m/s/yr)	0.20 (0.21)
Peak gradient (mmHg/yr)	6.5 (7.2)
Aortic valve area (cm^2/yr)	-0.08 (0.11)
Progression of calcification (Computed Tomography)	**n = 133**
Absolute change AVC score (AU/yr)	1608 (1865)
Per cent change absolute AVC score (%/yr)	29 (30)
Log AVC score (LogAU)	0.09 (0.10)

Variables stated as mean (standard deviation).
AVC - aortic valve calcium; Log - logarithm.

TABLE 6.3 Predictors of Disease Progression

	Change in peak velocity (m/s/yr)		Change in absolute AVC score (AU/yr)		Change in Log AVC score (LogAU/yr)		Per cent change in AVC score (%/yr)	
	R	p	R	p	R	p	R	P
Baseline demographics								
Age (years)	+0.24	**0.006**	+0.21	**0.02**	-0.10	0.24	-0.03	0.71
Height	-0.19	**0.03**	+0.23	**0.01**	-0.15	0.09	-0.12	0.19
Weight	-0.13	0.15	+0.12	0.18	+0.05	0.56	+0.17	0.06
Baseline disease severity								
Peak velocity	+0.32	**<0.001**	+0.48	**<0.001**	-0.05	0.60	-0.02	0.80
Absolute AVC score	+0.25	**0.004**	+0.49	**<0.001**	-0.26	**0.003**	-0.30	**<0.001**
Log AVC score	+0.26	**0.003**	+0.47	**<0.001**	-0.32	**<0.001**	-0.40	**<0.001**
Disease progression								
Change peak velocity/yr			+0.27	**0.002**	-0.02	0.83	+0.05	0.58
Change absolute AVC/yr	+0.27	**0.002**			+0.2	**0.02**	+0.27	**0.002**
Change log AVC/yr	-0.01	0.88	+0.20	**0.02**			+0.94	**<0.001**
Per cent change AVC/yr	+0.05	0.54	+0.27	**0.002**	+0.94	**<0.001**		
Blood pressure (mmHg)								
Baseline systolic BP	-0.04	0.68	-0.01	0.94	+0.14	0.11	+0.19	**0.03**
Baseline diastolic BP	+0.04	0.67	+0.05	0.59	+0.13	0.15	+0.13	0.15
Mean study systolic BP	<-0.01	0.98	-0.01	0.92	+0.06	0.48	+0.18	**0.04**
Mean study diastolic BP	+0.11	0.22	+0.03	0.71	+0.06	0.46	+0.11	0.20
Baseline serum biochemistry								
Urea (mmol/L)	-0.12	0.15	-0.07	0.41	+0.08	0.33	+0.20	**0.02**
Creatinine (μmol/L)	<-0.01	0.95	-0.04	0.62	-0.06	0.49	-0.07	0.39
Calcium (mmol/L)	+0.02	0.86	-0.12	0.17	-0.03	0.77	+0.21	**0.02**
Total cholesterol (mmol/L)	+0.14	0.10	-0.11	0.22	-0.03	0.75	-0.07	0.40
HDL cholesterol (mmol/L)	+0.16	0.06	+0.12	0.17	+0.17	0.05	+0.16	0.06
LDL cholesterol (mmol/L)	+0.11	0.21	-0.10	0.27	-0.06	0.51	-0.11	0.20
Mean on treatment serum biochemistry								
Urea (mmol/L)	-0.05	0.59	-0.02	0.79	-0.09	0.33	+0.06	0.48
Creatinine (μmol/L)	-0.14	0.10	<-0.01	0.99	-0.08	0.38	-0.05	0.58
Calcium (mmol/L)	+0.11	0.22	-0.10	0.25	+0.20	**0.02**	+0.24	**0.007**
Total cholesterol (mmol/L)	+0.05	0.58	-0.02	0.79	-0.09	0.33	-0.10	0.24
HDL cholesterol (mmol/L)	+0.14	0.11	+0.14	0.10	+0.14	0.10	+0.14	0.10
LDL cholesterol (mmol/L)	+0.03	0.70	-0.03	0.71	-0.11	0.23	-0.12	0.17
C-reactive protein								
Log baseline CRP	-0.14	0.11	-0.13	0.12	-0.17	0.05	-0.15	0.09
Log mean study CRP	-0.10	0.25	-0.04	0.62	-0.15	0.08	-0.13	0.15
Change log CRP/year	+0.07	0.42	+0.01	0.91	-0.04	0.68	+0.03	0.75
Brain natriuretic peptide								
Log baseline BNP	+0.26	**0.003**	+0.11	0.21	-0.17	0.06	-0.08	0.36
Change log BNP/year	+0.26	**0.002**	+0.32	**<0.001**	-0.05	0.61	+0.05	0.57

AVC - aortic valve calcium; Log - logarithm; BP - blood pressure; HDL - high-density lipoprotein; LDL - low-density lipoprotein; CRP - C-reactive protein; BNP - brain natriuretic peptide.

TABLE 6.4 Influence of clinical risk factors on measures of disease progression

	Change in peak velocity (m/s/yr)			Change in absolute AVC score (AU/yr)			Change in Log AVC score (LogAU/yr)			Per cent change in AVC score (%/yr)		
Risk Factor	No	Yes	p value	No	Yes	p value	No	Yes	p value	No	Yes	p value
Hyperlipidaemia	0.19 (n=125)	0.31 (n=9)	0.05	1607 (n=124)	1614 (n=9)	0.99	0.09 (n=123)	0.11 (n=9)	0.70	29.0 (n=122)	31.7 (n=9)	0.80
Hypertension	0.16 (n=65)	0.24 (n=69)	**0.03**	1408 (n=65)	1798 (n=68)	0.23	0.09 (n=64)	0.10 (n=68)	0.58	23.4 (n=63)	34.7 (n=68)	**0.03**
Ischaemic Heart Disease	0.21 (n=112)	0.15 (n=22)	0.20	1718 (n=112	1013 (n=21)	0.11	0.10 (n=111)	0.08 (n=21)	0.41	30.5 (n=110)	22.4 (n=21)	0.26
Diabetes Mellitus	0.20 (n=130)	0.18 (n=4)	0.82	1612 (n=129)	1472 (n=4)	0.88	0.09 (n=128)	0.06 (n=4)	0.57	29.6 (n=127)	18.3 (n=4)	0.47
PVD and, or CVD	0.19 (n=106)	0.24 (n=28)	0.32	1757 (n=117)	516 (n=16)	**0.01**	0.09 (n=116)	0.09 (n=16)	0.99	29.6 (n=118)	26.2 (n=13)	0.70
Current Smoker	0.21 (n=105)	0.17 (n=29)	0.34	1794 (n=103)	966 (n=30)	**0.03**	0.10 (n=103)	0.07 (n=29)	0.12	30.4 (n=102)	25.0 (n=29)	0.40
Male Sex	0.27 (n=38)	0.17 (n=96)	**0.02**	1027 (n=37)	1831 (n=96)	**0.03**	0.10 (n=37)	0.09 (n=95)	0.66	36.2 (n=37)	26.5 (n=94)	0.10

AVC - aortic valve calcium; PVD - peripheral vascular disease; CVD - cerebrovascular disease.

Progression of valvular calcification was predicted by the baseline AVC score ($p<0.001$) and the rate of change in log BNP per year ($p<0.001$). Age ($p=0.02$), height ($p=0.009$), mean study systolic blood pressure ($p=0.04$) and serum calcium concentrations ($p=0.02$) and the presence of hypertension ($p=0.03$) also correlated with progression in aortic valve calcification (Tables 6.3 and 6.4).

There was a weak negative correlation with smoking ($p=0.03$), the presence of vascular disease ($p=0.01$) and male sex ($p=0.03$). Progression in aortic jet velocity was not associated with the presence of hyperlipidaemia, ischaemic heart disease, smoking, or any of the biochemical markers of atherosclerosis (Tables 6.3 and 6.4). Furthermore, neither progression in aortic jet velocity ($r=0.03$, $p=0.70$) nor AVC score ($r=-0.11$, $p=0.23$) correlated with mean on treatment serum LDL cholesterol concentrations [Cowell *et al* 2005].

6.4.1.1 *Inflammation*

At baseline, serum CRP concentrations were the same in both treatment groups ($p=0.76$), but fell with 80 mg of atorvastatin ($p=0.001$). Baseline CRP concentrations did not correlate with baseline severity of stenosis (aortic jet velocity, $p=0.95$), or extent of valvular calcification (log AVC score, $p=0.82$). Furthermore neither baseline nor mean on treatment CRP concentrations correlated with disease progression or clinical outcome (Table 6.3).

6.4.1.2 *Arterial stiffness*

Augmentation pressure and pulse pressure, but not augmentation index, correlated with age, height, systolic blood pressure, and mean arterial pressure. No measures of arterial stiffness correlated with baseline severity of aortic valve stenosis or valvular calcification, nor were there any associations between arterial stiffness and disease progression.

6.4.1.3 *Brain natriuretic peptide*

Serum BNP concentrations at baseline were the same in both treatment groups (p=0.37) and were not influenced by atorvastatin therapy (p=0.33). However, serum BNP concentrations at baseline did correlate with baseline severity of stenosis (r=0.27, p=0.002) as well as with the extent of valvular calcification on CT (r=0.18, p=0.04). The progression in aortic jet velocity correlated with basal and rate of change in serum BNP concentrations (r=0.26, p=0.003 and r=0.26, p=0.002 respectively).

6.4.2 CLINICAL OUTCOME

During the study follow-up period, 43 patients (28%) reached a pre-defined clinical end-point (Table 6.5). Six patients died, 2 secondary to malignant disease. The remaining 4 were cardiovascular deaths; one patient with severe asymptomatic aortic stenosis collapsed and died of an acute myocardial infarction (diagnosed at postmortem), one patient with severe symptomatic aortic stenosis who had declined surgery had a sudden cardiac death, and 2 patients died in hospital whilst awaiting urgent valve replacement for severe symptomatic stenosis associated with heart failure.

TABLE 6.5 Clinical end-points

Clinical end-points	Number n = 155	Per cent %
Deaths	**6**	**3.8**
Cardiovascular	4	
Other	2	
Aortic valve replacement	**30**	**19.4**
Severe symptomatic aortic stenosis	28	
Severe asymptomatic aortic stenosis prior to non-cardiac surgery	1	
Aortic root dilatation and mild aortic stenosis	1	
Severe symptomatic aortic stenosis	**7**	**4.5**
Referred for AVR	5	
For medical management	2	
Total number end-points reached	**43**	**27.7**

AVR - aortic valve replacement.

Thirty patients underwent AVR, 28 of which were for severe symptomatic aortic stenosis. One patient underwent AVR for severe but asymptomatic aortic stenosis prior to lung resection, and another for mild aortic stenosis and a dilated aortic root.

Seven further patients developed symptoms secondary to severe aortic stenosis, of whom five were awaiting valve surgery at the time of study completion. The remaining 2 patients were deemed unfit for major cardiac surgery due to frailty and co-morbidity.

Overall fewer clinical end-points appeared to have been reached in the statin treated group, however numbers were small and the difference was not statistically significant (Chapter 4) [Cowell *et al* 2005]. Clinical outcome was only predicted by baseline and subsequent rate of progression of aortic stenosis severity and calcification ($p < 0.001$), as well as by baseline ($p=0.02$) and rate of progression ($p<0.001$) of serum BNP concentrations. However, neither clinical nor biochemical markers of atherosclerosis and cardiovascular risk, including serum cholesterol and CRP concentrations were associated with clinical outcome (Table 6.6 and 6.7).

Table 6.6 Predictors of clinical outcome

	No Event	Event	*t*-test P value
Baseline demographics			
Age (years)	67(11)	69(9)	0.47
Height (cm)	168	169	0.46
Weight (Kg)	79(15)	81(15)	0.41
Blood Pressure			
Baseline systolic BP	145(20)	141(18)	0.19
Baseline diastolic BP	82(11)	81(11)	0.36
Mean study systolic BP	143(18)	138(16)	0.14
Mean study diastolic BP	81(8)	80(11)	0.77
Disease severity			
Baseline Vmax	3.20 (0.53)	4.0 (0.54)	**<0.001**
Baseline CT AVC	6686 (7351)	11401 (9081)	**0.001**
Baseline Log CT AVC	3.57 (0.55)	3.93 (0.35)	**<0.001**
Disease progression			
Change peak velocity/yr	0.13 (0.16)	0.37 (0.21)	**<0.001**
Change absolute AVC/yr	1129 (1328)	2850 (2429)	**<0.001**
Change log AVC/yr	0.09 (0.12)	0.10 (0.06)	0.68
Per cent change AVC/yr	28.7 (32.7)	30.7 (23.6)	0.73
Baseline serum biochemistry			
Urea (mmol/L)	6.7(5.8)	6.1(1.7)	0.52
Creatinine (μmol/L)	92(22)	92(19)	0.86
Calcium (mmol/L)	2.29(0.11)	2.29(0.10)	0.97
Total cholesterol (mmol/L)	5.7(0.9)	5.7(1.1)	0.98
HDL cholesterol (mmol/L)	1.5(0.5)	1.6(0.4)	0.25
LDL cholesterol (mmol/L)	3.5(0.8)	3.5(1.0)	0.96
Mean on treatment serum biochemistry			
Urea (mmol/L)	6.2(1.9)	6.2 (1.7)	0.96
Creatinine (μmol/L)	92 (21)	93 (24)	0.68
Calcium (mmol/L)	2.29 (0.09)	2.29 (0.10)	0.86
Total Cholesterol (mmol/L)	4.6 (1.3)	4.7 (1.5)	0.86
HDL cholesterol (mmol/L)	1.4 (0.4)	1.5 (0.4)	0.26
LDL cholesterol (mmol/L)	2.8 (1.2)	2.8 (1.3)	0.83
C-reactive protein			
Log baseline CRP	0.42 (0.50)	0.32 (0.48)	0.32
Log mean study CRP	0.28(0.54)	0.41(0.52)	0.23
Change log CRP/year	-0.08(0.18)	0.03(0.33)	**0.016**
Brain natriuretic peptide			
Log baseline BNP	2.30 (0.56)	2.54 (0.38)	**0.02**
Rate of change BNP/yr	0.08 (0.13)	0.18 (0.20)	**<0.001**

Variables stated as mean (SD).
BP - blood pressure; Vmax - peak velocity; CT - computed tomography; AVC - aortic valve calcium; HDL - high-density lipoprotein; LDL - low-density lipoprotein; CRP - C-reactive protein; Log - logarithm; BNP - brain natriuretic peptide.

TABLE 6.7 Clinical risk factors predicting clinical outcome

Clinical Risk Factors	No Event (n = 112)	Event (n = 43)	Chi^2-test p value
Hyperlipidaemia	7 (6)	3 (7)	0.89
Hypertension	56 (50)	23 (53)	0.83
Ischaemic heart disease	23 (20)	7 (16)	0.71
Diabetes mellitus	3 (3)	2 (5)	0.91
Peripheral and, or cerebrovascular disease	21(19)	9 (21)	0.94
Current smoker	28 (25)	5 (12)	0.11
Male sex	78(70)	30 (72)	0.93

Categorical variables stated as, n (%).

6.5 DISCUSSION

Using a cohort of patients with aortic stenosis, we have prospectively demonstrated that the major predictors of disease progression and clinical outcome remain measures of disease severity; namely aortic jet velocity, aortic valve calcification and serum BNP concentration. With the exception of hypertension, the presence of atherosclerotic risk factors and vascular disease were not predictive.

It is clear that patients with symptomatic aortic stenosis require urgent aortic valve surgery. The timing of surgery in patients with asymptomatic severe aortic stenosis remains controversial and clinical practice varies. Given the morbidity and mortality associated with valve surgery, many argue that surgery should be delayed until the onset of symptoms. The concern is that patients do not always accurately report the onset of symptoms. This may arise because patients do not recognise the significance of symptoms, particularly mild dyspnoea or fatigue that may be wrongly attributed to age, or subconsciously reduce activity levels in order to avoid symptoms. It would therefore be useful to have biochemical or clinical markers that help identify those patients with severe disease who might benefit from prompt aortic valve surgery.

6.5.1 C-REACTIVE PROTEIN

Serum CRP concentration is a sensitive but non-specific marker of systemic inflammation that is elevated in patients with vascular disease [Van der Meer *et al* 2002]. It is an independent predictor of future cardiovascular events in healthy adults and in those with established disease [Ridker *et al* 1998]. Furthermore serum CRP concentrations are elevated in patients with calcific aortic stenosis, even in the

absence of other overt vascular disease [Galante *et al* 2001]. In severe aortic stenosis, valvular CRP concentrations correlate with serum CRP concentrations [Skowash *et al* 2006], and serum CRP concentrations fall following AVR [Gerber *et al* 2003]. This is in keeping with histological studies suggesting that the aortic valve is a site of active inflammation. Could serum CRP concentrations provide a marker to predict disease progression or clinical outcome in patients with calcific aortic stenosis?

Serum CRP concentrations do not correlate with the severity of aortic stenosis [Gunduz *et al* 2003] and no study has to date evaluated its relationship with clinical outcome. One preliminary study has suggested that disease progression was more rapid in those with higher CRP concentrations [Sanchez *et al* 2006] but conclusions were limited by the small sample size (n=~20 per group), length of follow-up (6 months) and the single baseline CRP measurement. We have here looked at relationship between serum CRP concentrations and (a) the severity of valvular stenosis at baseline, (b) the rate of disease progression, and (c) clinical outcome. We were unable to demonstrate any association between serum CRP concentrations and any of these measures despite being able to reproduce the well-described reductions of serum CRP concentrations with atorvastatin therapy in our patient group [Houslay *et al* 2006].

6.5.2 ARTERIAL STIFFNESS

Decreased vascular distensibility is a marker of arterial disease and is associated with increased cardiovascular risk. Arterial stiffness increases with age [Mitchell *et al* 2004] and smoking [Mahmud and Feely 2003], and is associated with certain disease states including atherosclerosis [van Popele *et al* 2001], hypertension [Laurent *et al*

1994], coronary artery disease [Hayashi *et al* 2002] diabetes mellitus [Salomaa *et al* 1995], and hypercholesterolaemia [Wilkinson *et al* 2002]. Clinical studies demonstrate that increased arterial stiffness is an independent predictor of cardiovascular risk [Weber *et al* 2005], premature coronary artery disease [Weber *et al* 2004], and mortality in patients with hypertension [Laurent *et al* 2001] and end-stage renal failure [Blacher *et al* 1999; London *et al* 2001]. Little is known about the associations between aortic stenosis and arterial stiffness but given that calcific aortic stenosis is a condition associated with progressive rigidity and thickening of the aortic valve cusps [Newby *et al* 2006], we wished to explore whether there was a relationship between arterial stiffness and aortic stenosis and whether this could be used to predict disease progression or clinical outcome.

One small study (n=30) has previously suggested that invasive measurements of aortic pulse wave velocity correlate with the severity of aortic stenosis (Liu *et al* 2004). However, we were unable to find any association between non-invasive measures of arterial stiffness, and basal severity, disease progression or clinical outcome. In a limited number of patients (n=18), we did measure pulse wave velocity but again demonstrated no associations with disease severity, progression or outcome. This lack of association suggests that the pathophysiological processes underlying arterial stiffness and aortic stenosis are distinct and independent.

We do accept that we may have missed a weak association and that many of the principles and assumptions employed by pulse wave analysis to generate measures of arterial stiffness may not be valid in patients with aortic stenosis. Nevertheless, we

were able to confirm previous associations between measures of arterial stiffness and age, height and blood pressure.

6.5.3 BRAIN NATRIURETIC PEPTIDE

Brain natriuretic peptide is elevated in both symptomatic and asymptomatic left ventricular dysfunction, and serum concentrations correlate with NYHA class and prognosis [Tsutamoto *et al* 1997; McDonagh *et al* 2001; Berger *et al* 2002; Lubien *et al* 2002]. Serum BNP concentrations are also elevated in other structural heart disease [Nakamura *et al* 2002] including left ventricular hypertrophy and aortic stenosis. Recent studies have demonstrated that serum BNP concentrations correlate with the severity of aortic stenosis and NYHA class [Gerber *et al* 2003; Lim *et al* 2004]. In patients with severe aortic stenosis, BNP is an independent predictor of symptom free survival [Bergler-Klein *et* al 2004] and clinical outcome [Lim *et al* 2004].

We have established, for the first time, that basal and subsequent increases in serum BNP concentrations predict both disease progression and clinical outcome in a large cohort of patients. This predictive power is perhaps not unsurprising given that serum BNP concentrations correlate with the baseline severity of aortic stenosis, which in turn is a major predictor of disease progression and clinical outcome. It is likely therefore that serum BNP concentrations are acting as a marker of disease severity through the association with left ventricular hypertrophy and systolic dysfunction.

6.5.4 STUDY LIMITATIONS

In the SALTIRE trial, we excluded patients with coronary artery disease who were receiving or had an indication for statin therapy. Although atherosclerotic risk factors may have a more important role in the progression of aortic stenosis in these patients, they will require risk factor management irrespective of their valvular heart disease. Moreover, our patient population was representative of the population of patients with aortic stenosis seen in clinical practice with a broad age range and significant cardiovascular co-morbidity.

We have to date conducted only univariate analyses. Given the potential interdependency of some of the variables, a step-wise multiple logistic regression analysis is underway. This may help identify independent predictors of disease progression and clinical outcome, but is unlikely to alter our main conclusions.

6.6 CONCLUSIONS

The major predictors of disease progression and clinical outcome in patients with aortic stenosis remain measures of disease severity. Estimation of serum BNP concentration may be helpful in the monitoring of patients with severe aortic stenosis particularly where there is clinical uncertainty or where incomplete clinical information is available such as poor quality echocardiographic imaging.

CHAPTER 7

CONCLUSIONS AND FUTURE DIRECTIONS

7.1 CONCLUSIONS

7.1.1 HELICAL COMPUTED TOMOGRAPHY IN THE QUANTIFICATION OF AORTIC VALVE CALCIUM

Severity of valvular calcification has been reported to be a strong predictor of clinical outcome in patients with aortic stenosis. Echocardiography is the gold standard for assessing patients with valvular heart disease, but only provides a semi-quantitative measure of calcification. Computed tomography has recently been identified as a potential tool for more accurate quantification of AVC content. Electron beam CT derived calcium scores demonstrate good reproducibility with interscan variation of 7-9% [Pohle *et al* 2001; Budoff *et al* 2002], and correlate closely with calcium deposition in excised valvular tissue [Messika-Zeitoun *et al* 2004].

At inception of the SALTIRE trial, reproducibility of AVC scores quantified by helical CT had not been determined, nor had there been a direct comparison with electron beam CT. A number of studies quantifying coronary artery calcium content have subsequently demonstrated a good correlation between calcium scores determined using multi-slice and electron beam CT [Carr *et al* 2000; Becker *et al* 2001].

We have demonstrated that the measurement of AVC content using helical CT reveals very good interscan reproducibility when assessed in a cohort of 20 patients undergoing repeated assessment. Our figures indicate that helical CT is a useful tool

for determining the severity of valvular calcification and in monitoring the progression of calcium accumulation. This suggests that it may be valuable in assessing the influence of pharmacological therapy on disease progression.

7.1.2 Relationship between aortic valve calcium content and severity of aortic stenosis

In patients with aortic stenosis, disease progression and clinical outcome are influenced by baseline severity of stenosis, as well as the extent of valvular calcification [Davies and Gershlick 1991; Bahler *et al* 1999; Rosenhek *et al* 2000]. Until recently the relationship between the Doppler-derived severity of stenosis and extent of valve calcification was not clear. Calcification of the aortic valve reduces leaflet flexibility, with a resultant acceleration of blood flow across the narrowed orifice, and hence an increase in aortic jet velocity. It is important to remember that jet velocity will be determined by other factors influencing the haemodynamic load on the left ventricle including the presence of hypertension or coronary artery disease. Although an association between valve calcification and severity of stenosis seems likely, this had not been clearly demonstrated in a prospective trial.

We have prospectively demonstrated in a large cohort of patients that severity of stenosis determined by Doppler echocardiography is strongly correlated with the degree of aortic valve calcification on helical CT. This suggests that the CT derived calcium score provides complementary information to the jet velocity, and that AVC accumulation over time may provide additional prognostic information independent of the aortic jet velocity.

7.1.3 Influence of statin therapy on the progression of calcific aortic stenosis

Hydroxymethylglutaryl coenzyme A reductase inhibitors or statins are now well established in the primary and secondary prevention of coronary artery disease. Several studies have suggested that these drugs can cause regression of coronary artery disease as well as reduce the calcific volume of coronary plaques [Callister *et al* 1998]. Given the clinical association of calcific aortic stenosis with hyperlipidaemia and coronary artery disease, and the striking histological similarities with atheroma, the speculation that statins may have the potential to influence disease progression in aortic stenosis is an intriguing hypothesis [Mohler 2000].

Recent retrospective studies [Aronow *et a* 2001; Novaro *et al* 2001; Bellamy *et al* 2002; Rosenhek *et al* 2004] have suggested that statins may delay disease progression in aortic stenosis (Table 7.1) through their lipid-lowering and anti-inflammatory actions. These observational data should be interpreted with caution since none of these studies were prospective randomised trials, serum LDL cholesterol concentrations did not correlate with disease progression, and the statin doses were small. There may also be some publication bias with studies reporting negative findings under-represented in the literature [Samal *et al* 2002; Antonini-Canterin *et al* 2005].

TABLE 7.1 Summary of trials assessing progression of aortic stenosis by repeated echocardiography

	Aronow *et al*	Novaro *et al*	Bellamy *et al*	Rosenhek *et al*	Samal *et al*	Antonini-Canterin *et al*	Cowell *et al*
Design	**Retrospective Observational**	**Retrospective Observational**	**Retrospective Observational**	**Retrospective Observational**	**Retrospective Observational**	**Retrospective Observational**	**Prospective Randomised Controlled Trial**
Patients	180	174	156	211	112	242	134
Patients on statin	62	57	38	50	55	121	65
Mean age (yr)	82	68	77	70	73	68	68
Mean follow-up (months)	33	21	44	24	-	54	25
Total cholesterol (mmol/L)	-	5.5	5.8	5.8	-	-	5.7
Correlation of progression with LDL cholesterol	-	Yes/No	No	No	Yes	No	No
Reduce progression with statin therapy	Yes	Yes	Yes	Yes	No	No	No

LDL - low-density lipoprotein.

The SALTIRE trial [Cowell *et al* 2005] is the first double-blind randomised controlled trial of lipid-lowering therapy to be completed in patients with calcific aortic stenosis. This trial of 155 patients demonstrated that, whilst atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations, it did not halt the progression or induce regression of the valvular disease process as measured by both Doppler echocardiography and helical CT. Indeed no relationship between serum LDL cholesterol concentrations and the progression of aortic stenosis was apparent, nor was there a demonstrable effect of high dose atorvastatin on clinical end-points. Thus, irrespective of the method of assessing disease progression, we have consistently demonstrated the continued deterioration of aortic stenosis despite intensive reductions in serum cholesterol concentrations.

7.1.4 Influence of statin therapy on the progression of coronary artery calcification

Coronary artery calcification is an independent risk factor for coronary heart disease, and progresses over time at a rate of 20-30% per year [Callister *et al* 1998; Budoff *et al* 2000; Schmermund *et al* 2001]. Calcium burden may be determined using CT, and quantity of coronary artery calcium correlates with overall coronary plaque burden [Mautner *et al* 1994; Rumberger *et al* 1995; Sangiorgi *et al* 1998]. Several non-randomised observational studies have reported a reduction in coronary calcium accumulation in patients taking statin therapy [Callister *et al* 1998; Achenbach *et al* 2002], but no placebo-controlled trials have been published substantiating these results.

In using helical CT to determine AVC content in the SALTIRE trial, we had the opportunity to assess prospectively the effect of intensive lipid-lowering therapy on coronary calcification. We demonstrated good reproducibility of coronary scores and progression of coronary artery calcification by 20% per year. However, intensive lipid-lowering therapy did not delay the progression or induce regression of coronary artery calcium burden. This is despite a 50% reduction in serum LDL cholesterol and CRP concentrations.

Our findings indicate that earlier observational studies have overestimated the potential beneficial effects of statins on coronary artery calcification, and indeed more recent prospective randomised controlled trials [Arad *et al* 2005; Raggi *et al* 2005] have also failed to find an effect. Although coronary artery calcium scores correlate well with the presence of atherosclerosis and predict future coronary risk, our findings indicate that there is currently no role for monitoring progression of coronary artery calcification to assess the effects of lipid-lowering therapy out with a clinical trial setting.

7.1.5 Factors influencing the progression of aortic stenosis and clinical outcome

Calcific aortic stenosis is common, and gradually progresses over time. Rates of disease progression vary widely between individuals, and as soon as patients with severe stenosis develop symptoms, AVR is indicated. In general, patients with milder forms of disease have a better outlook, but there is an increased risk of unrelated cardiovascular events.

Mechanical injury is thought to initiate the disease process, inducing endothelial disruption that is followed by an inflammatory process closely resembling atherosclerosis. In keeping with this observation, the clinical risk factors for aortic stenosis include those for cardiovascular disease, as well as conditions affecting calcium metabolism. However, the clinical factors associated with disease progression are less well defined, with many mainly retrospective studies reporting conflicting outcomes. Clinical outcome, however, is strongly predicted by baseline aortic jet velocity, rate of change in jet velocity, the extent of valvular calcification and functional status [Otto *et al* 1997; Rosenhek *et al* 2000]. We wished to define predictors of disease progression and clinical outcome more clearly, and to identify new modifiable markers.

In patients with calcific aortic stenosis we have prospectively demonstrated that the major predictors of disease progression and clinical outcome remain measures of disease severity; namely aortic jet velocity, aortic valve calcification and serum BNP concentration. With the exception of hypertension, the presence of atherosclerotic risk factors and vascular disease were not predictive.

We have established, for the first time, that basal and subsequent increases in serum BNP concentrations predict both disease progression and clinical outcome in a large cohort of patients. This predictive power is perhaps not unsurprising given that serum BNP concentrations correlate with the baseline severity of aortic stenosis, which in turn is a major predictor of disease progression and clinical outcome. It is likely therefore that serum BNP concentrations are acting as a marker of disease

severity through the association with left ventricular hypertrophy and systolic dysfunction.

7.2 FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

7.2.1 COMPUTED TOMOGRAPHY IN THE ASSESSMENT OF AORTIC VALVE CALCIFICATION AND STENOSIS

Although we have clearly demonstrated that helical (two detector array, or double-helix) CT is a reproducible means of measuring valvular calcium content, it is unlikely that such scanners will be utilised in the future given rapid technological advances that have taken place in recent years. Factors influencing the reproducibility of calcium scores include cardiac and respiratory motion artefact, method of image acquisition and reconstruction, the use of phantom calibration, and the method of calcium score calculation. The latest multi-slice scanners with up to 64 detector arrays acquire multiple images at different levels simultaneously in sub-second time, and reconstruct images using ECG gating. Movement artefact and partial-volume effects are reduced [Willmann *et al* 2002; Morgan-Hughes *et al* 2003], and it seems logical to assume that more accurate quantification of valvular calcification and improved specificity will result.

Alternative methods of quantifying calcification have been evaluated, including volume and mass scores that have been shown to improve the reproducibility of coronary calcium scores [Callister *et al* 1998]. These scoring methods have also been utilised in recent aortic valve studies [Morgan-Hughes *et al* 2003; Koos *et al* 2005],

but further evaluation is required to determine which is the most reproducible using the very latest scanning equipment.

Computed tomography imaging has improved to the extent that direct measurement of aortic stenosis severity is now also possible. Valve area determined by planimetry, is comparable to that derived by transthoracic and transoesophageal echocardiography [Alkadhi *et al* 2006; Feuchtner *et al* 2006]. Given the radiation doses involved, it is unlikely that CT will supersede echocardiography in the assessment of stenosis severity, it may however, prove a useful non-invasive technique in patients with poor ultrasound images.

7.2.2 Potential therapies or aortic valve stenosis

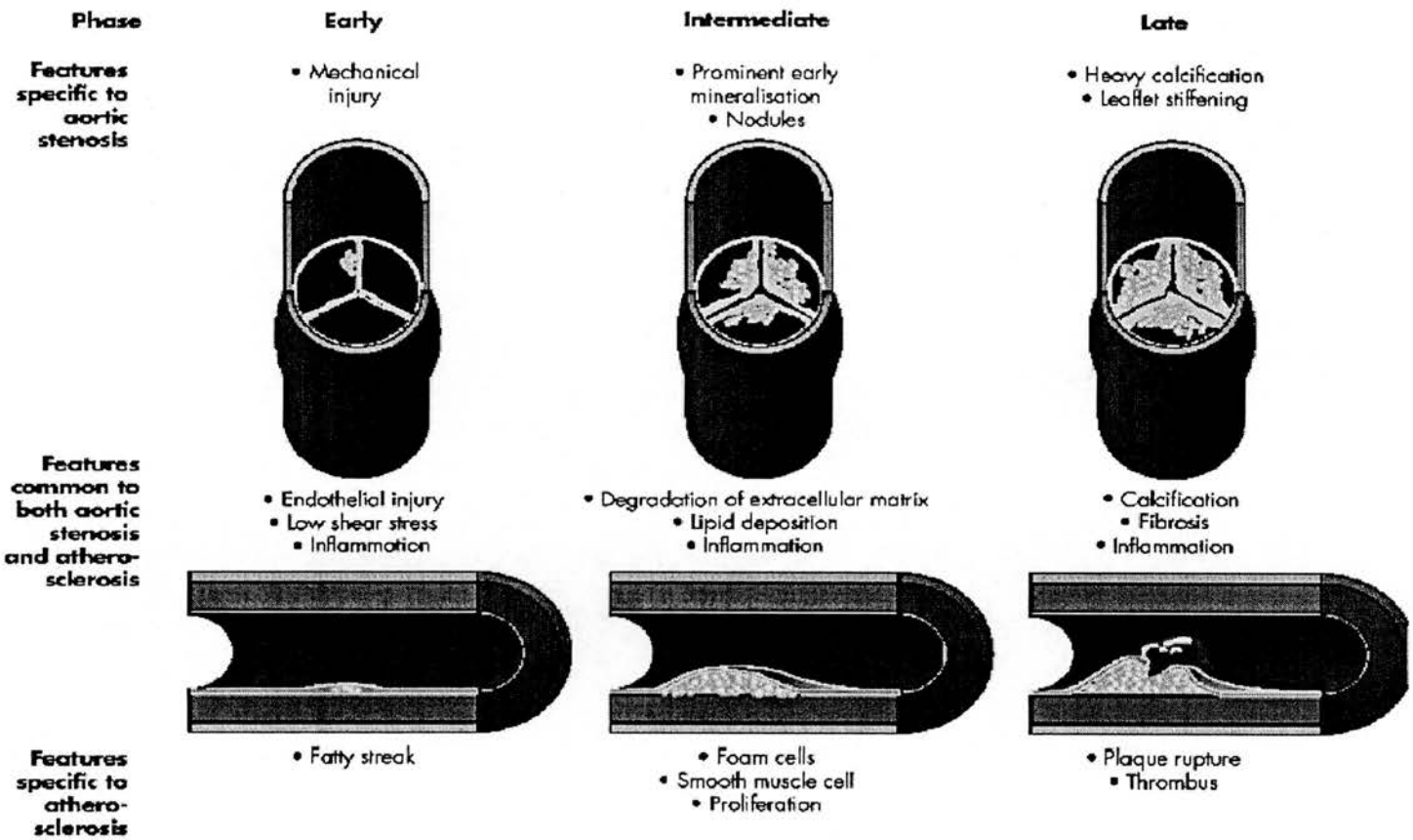
The current management of patients with aortic stenosis includes monitoring disease progression, and ensuring patient awareness of the need for antibiotic prophylaxis against the relatively low risk of infective endocarditis. For those patients with severe symptomatic disease, AVR is a priority with conventional medical therapy reserved for symptom control in inoperable cases. However, the majority of patients with aortic stenosis do not have symptoms or an indication for surgery. Are there any interventions that can halt or slow the progression of the disease process? Theoretically, anti-inflammatory and anti-proliferative agents would be anticipated to alter the natural history of aortic stenosis. Statin and ACE inhibitor therapies are two commonly used treatments that have proven secondary preventative benefits in cardiovascular disease and exhibit some of these desirable anti-inflammatory and anti-proliferative properties.

7.2.2.1 *Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins)*

In the SALTIRE trial, intensive lipid-lowering therapy with 80 mg atorvastatin daily did not halt the progression or induce regression of calcific aortic stenosis. Given the data linking aortic stenosis with atherosclerosis and hypercholesterolaemia, this result is surprising. One potential explanation is that, whilst these features may drive the initiation of aortic stenosis, disease progression may be dependent upon other factors. The aortic valve is subject to continuous dynamic mechanical stress, and leaflet plasticity and structure can have an overriding influence, such as with a bicuspid valve. Moreover, in contrast to atherosclerosis (Figure 7.1), aortic stenosis is associated with a virtual absence of smooth muscle cell proliferation and lipid-laden macrophages, and dominated by earlier and more extensive mineralisation. Decreasing the lipid pool and increasing the fibrous cap may be less relevant to the progression of aortic stenosis than it is for the reduction in atherosclerotic plaque rupture with statin therapy in patients with coronary heart disease. Whilst stabilisation and calcification of plaques is beneficial and reduces cardiovascular events in patients with coronary artery disease, reduced inflammation, promotion of healing and increased calcification may lead to progression of aortic stenosis.

It could be argued that lipid-lowering therapy is unlikely to influence disease progression in the presence of significant aortic stenosis. Patients with aortic velocities below 2.5 m/s were excluded from the SALTIRE trial and intervening at

Figure 7.1 Common and specific pathogenic features of aortic stenosis and atherosclerosis.



this earlier stage of the disease process may have been more beneficial. However, such patients do not commonly present to routine clinical practice and their identification would potentially require population screening. Moreover, the SALTIRE trial was unable to exclude a modest treatment benefit (a delay in disease progression of <0.07 m/s/yr or <5% aortic valve calcification/yr). Although such modest reductions are unlikely to be meaningful in the majority of older patients, a small decrease in disease progression may be clinically important in younger patients with mild disease who may progress over many years. Indeed, a small preliminary observational study suggests that statin therapy may reduce disease progression in patients with aortic sclerosis [Antonini-Canterin *et al* 2005] and this finding warrants prospective evaluation.

Statin therapy in patients with aortic stenosis may confer secondary preventative benefits that are independent of its effects on the valvular disease process because of the association between aortic stenosis and coronary artery disease. The SALTIRE trial was not powered to assess the benefits of lipid-lowering therapy on cardiovascular end-points, such as non-fatal and fatal myocardial infarction, but there was a trend in favour of reduced clinical events. It is likely that aortic stenosis and sclerosis may be important markers of occult vascular disease and thereby identify patients who would gain from the preventative benefits of statin therapy. Several larger clinical end-point trials (including the SEAS and ASTRONOMER trials [Rajamannan 2006]) are currently underway that will be able to address this issue.

Finally, for many patients with aortic stenosis, the first symptom to develop is chest pain and this precipitates the decision to undertake AVR. However, this may be driven by concomitant coronary artery disease rather than progression of valvular stenosis. Previous secondary prevention trials in coronary heart disease have reported a reduction in coronary artery bypass graft surgery rates [The Heart Protection Study Collaborative Group 2002]. Thus, the larger clinical end-point trials of statin therapy in aortic stenosis may suggest a reduction in the rate of valve surgery but this may be driven by patients with aortic stenosis who undergo combined aortic valve and bypass surgery for symptoms of angina pectoris. If statin therapy truly reduces disease progression then a reduction in isolated AVR would be anticipated.

At present we cannot recommend the use of statin therapy in patients with isolated aortic stenosis in the absence of other cardiovascular risk factors. Indeed recently published American Heart Association and American College of Cardiology guidelines suggest awaiting the outcome of further prospective trials in patients with mild disease that are followed up for a longer period [Bonow *et al* 2006]. Furthermore, evaluation of the effects of statins in younger patients with aortic valve sclerosis, prior to the development of significant haemodynamic change and progression to valve stenosis, will be required.

7.2.2.2 *Angiotensin-converting enzyme inhibition*

There are several reasons to believe that ACE inhibitor therapy may have a role in the management of patients with aortic stenosis. First, in contrast to normal valves, sclerotic aortic valves have demonstrable tissue expression of angiotensin II and

ACE [Helske *et al* 2004; O'Brien *et al* 2005] and these may contribute to valvular inflammation, calcification and disease progression. Second, the pressure overload induced by aortic stenosis has several effects on the myocardium including left ventricular hypertrophy, apoptosis and fibrosis. This may accelerate the left ventricular systolic and diastolic dysfunction associated with aortic stenosis. Animal models of outflow obstruction using aortic banding have demonstrated improvement in diastolic function [Litwin *et al* 1995] and survival [Weinberg *et al* 1994; Turcani and Rupp 2000] with ACE inhibitor treatment, and in patients with aortic stenosis intra-coronary infusion of ACE inhibitor resulted in immediate improvement in diastolic function [Friedrich *et al* 1994]. This suggests that ACE inhibitors have the potential to influence clinical outcome through their effect on left ventricular diastolic function and remodelling. Finally, blood pressure lowering will indirectly reduce the pressure overload of the left ventricle as well as potentially reduce the mechanical stress and strain on the aortic valve.

Two preliminary observational studies with ACE inhibitor therapy in patients with aortic stenosis have been conflicting. In a retrospective analysis of 211 patients, Rosenhek and colleagues [Rosenhek *et al* 2004] failed to demonstrate a delay in the progression of aortic stenosis in patients maintained on ACE inhibitor therapy. Furthermore, the presence of hypertension did not appear to influence the outcome. In contrast, O'Brien and colleagues [O'Brien *et al* 2005] found that ACE inhibitor therapy was associated with a 71% reduction in the progression of aortic valve calcification in 123 patients with aortic stenosis undergoing electron beam CT.

However, such retrospective observational data are difficult to interpret and the study findings have wide confidence intervals.

Historically, ACE inhibition was said to be contraindicated in patients with aortic stenosis. This has primarily been due to the concern of invoking profound peripheral vasodilatation that would result in haemodynamic compromise, collapse and potentially death. However, ACE inhibitors are very well tolerated when initiated in patients with aortic stenosis [Chockalingham *et al* 2004; O'Brien *et al* 2004] and many patients (~30%) with aortic stenosis are unknowingly established on such therapy without compromise. Indeed, the use of ACE inhibitors appears to confer long-term survival benefit in patients considered to have a contraindication including those with aortic stenosis [Ahmed *et al* 2005]. The potential beneficial haemodynamic and cardiac effects of ACE inhibition are increasingly being recognised [Routledge and Townsend 2001] and warrant further study in patients with aortic stenosis.

7.2.3 Statin therapy and coronary artery calcification

Despite the evidence that statin therapy is extremely successful in the primary and secondary prevention of cardiovascular disease, we have not demonstrated a beneficial effect of statin therapy on coronary artery calcification. It has been suggested that calcified atherosclerotic plaques may be relatively more stable [Mintz *et al* 1995], indicating a possible protective role of calcification in coronary plaques. Statin therapy is thought to produce many of its beneficial effects through plaque stabilisation. Thus vascular calcification may play a role in the initial stabilisation of

atherosclerotic plaques. This is consistent with our findings and would account for the lack of effect on the progression of coronary artery calcification despite a reduction in serum CRP concentrations.

After the initial stabilisation of the atherosclerotic plaque, it would be anticipated that subsequent progression of coronary calcification would be inhibited. The present study was brief, and follow-up was only continued for a median of 2 years. It would be important to extend our observations to 5 or more years to assess properly the impact of statin therapy on the long-term progression of coronary artery calcification. However, it should be acknowledged that the clinical benefits of statin therapy are apparent within the first few years [Lewis *et al* 1998; The LIPID Study Group 1998; The Heart Protection Study Collaborative Group 2002] and in some cases the first few months [Schwartz *et al* 1998] of therapy. Moreover, the St Francis Heart Study demonstrated no beneficial effects despite 4.3 years of follow-up [Arad *et al* 2005].

7.2.4 Disease progression and clinical outcome in calcific aortic stenosis

Aortic stenosis is the commonest adult heart valve condition seen in the western world. It is a gradually progressive disease, characterised by a long asymptomatic phase, followed by a shorter symptomatic phase usually associated with severe narrowing of the aortic valve orifice. Despite the favourable outlook in those patients with mild asymptomatic disease, there is an increased risk of cardiovascular events unrelated to the aortic valve disease.

Historically, calcific aortic stenosis has been attributed to prolonged "wear and tear" and age-associated valvular degeneration. However, recent evidence suggests that calcific aortic stenosis may result from an active inflammatory process resembling atherosclerosis (Figure 7.1) but also involving biochemical, humoral and genetic factors. Endothelial injury or disruption is thought to allow lipids to penetrate the valvular interstitial tissue [O'Brien *et al* 1996] and accumulate in areas of inflammation [O'Brien *et al* 1996; Olsson *et al* 1999]. Mineralisation is a characteristic of both atherosclerotic and aortic valve lesions, and arises in close proximity to areas of inflammation. Histological studies have highlighted the common features but also confirmed differences in the cellular and mineral components of the two lesions.

These differences may, in part, explain why only 40% of patients with severe aortic stenosis have significant coronary artery disease [Peltier *et al* Cardiol 2003] and why the majority of patients with coronary artery disease do not have aortic stenosis. As the underlying pathology for the two conditions appears to be similar, it is likely that other unknown factors, including genetic factors, influence the development of valvular as opposed to vascular lesions [Otto and O'Brien 2001].

Predictors of disease progression have not previously been clearly defined. We have now prospectively demonstrated that the strongest predictors of both disease progression and clinical outcome are baseline severity of stenosis, BNP and extent of valve calcification. The more severe the stenosis and the more heavily calcified the valve, the higher the BNP and the faster the rate of disease progression. However,

although severity of stenosis correlates with the extent of valvular calcification, the spectrum of calcification for a given aortic jet velocity varies widely, and this diversity is likely to be important in evaluating patients approaching the need for AVR.

7.2.5 FUTURE EVALUATION OF PROGRESSION AND CLINICAL OUTCOME

Our findings highlight the importance of evaluating stenosis severity, calcium burden and BNP in monitoring patients with aortic stenosis. Larger clinical trials are needed to evaluate their influence on clinical outcome. Identification of patients at highest risk will facilitate appropriate disease monitoring, with the potential to determine optimal timing of AVR and influence surgical outcome.

7.3 SUMMARY

Calcific aortic stenosis is no longer regarded as an age-related degeneration, but an active disease process. The need for an alternative to aortic valve replacement is highlighted by the rising prevalence of aortic stenosis. New therapeutic strategies to limit disease progression are needed in order to delay, and potentially avoid, the need for valve surgery. Statin and ACE inhibitor therapies are two potential and promising therapies that may have beneficial effects in patients with aortic stenosis. They may reduce cardiovascular events rather than disease progression *per se,* but may prove to be valuable preventative therapy. We must, however, await the results of ongoing large randomised controlled trials to define the role of statin therapy, and consider prospective trials of drugs influencing the renin-angiotensin system, and other anti-inflammatory agents including aspirin.

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Aortic Valve Calcification on Computed Tomography Predicts the Severity of Aortic Stenosis

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AIM: Incidental aortic valve calcification is often detected during computed tomography. The aim was to compare the severity of valvular stenosis and calcification in patients with aortic stenosis.
MATERIALS AND METHODS: One hundred and fifty-seven patients aged 68 ± 11 years (range: 34–85) with aortic valve stenosis underwent multislice helical computed tomography and Doppler echocardiography performed by independent, blinded observers. The aortic valve calcium score was determined using automated computer software calibrated with a phantom.
RESULTS: Doppler echocardiography demonstrated a post-valve velocity of 3.45 ± 0.66 m/s and a peak gradient of 49 ± 11 mmHg. Computed tomography showed excellent reproducibility and the median aortic valve calcium score was 5858 AU (interquartile range, 1555–14,596). The computed tomography aortic valve calcium score positively correlated with the Doppler post-valve velocity and peak gradient ($r = 0.54$, $p < 0.0001$ for both) of the aortic valve. All patients with severe aortic stenosis had a calcium score of >3700 AU.
CONCLUSION: Calcification of the aortic valve is closely associated with the severity of aortic stenosis, and heavy calcification suggests the presence of severe aortic stenosis that requires urgent cardiological assessment. Patients with lesser degrees of aortic valve calcification should be screened for aortic stenosis and monitored for disease progression. Cowell, S. J. *et al.* (2003). *Clinical Radiology* **58**: 712–716.

Key words: calcification, aortic valve, computed tomography, echocardiography.

INTRODUCTION

Calcific aortic stenosis is the commonest reason for valve replacement in the developed world. The condition may be due to progressive calcification of a congenitally bicuspid valve or "degenerative" calcification of a morphologically normal valve [1]. Irrespective of the aortic valve morphology, the histological features are surprisingly similar to those of coronary atheroma and include lipid deposition, fibrosis and calcification [2].

The rate of progression of aortic stenosis appears to be most rapid in those patients with severe calcific disease [3,4]. The annual increase in aortic valve gradient is more than twice that seen in patients with non-calcific disease (9.7 versus 4.4 mmHg/year) and the grade of calcification correlates with the rate of disease progression [5]. Indeed, moderate or severe aortic valve calcification is the strongest independent risk factor for an adverse clinical outcome with a five-fold increase in the rate of death or aortic valve replacement [4].

Computed tomography is being increasingly used as a non-invasive method of screening for atherosclerotic coronary artery disease [6,7] with 80–100% sensitivity and 80% specificity [8]. There is an association between coronary artery disease and calcific aortic stenosis, with approximately a third of patients with aortic stenosis having significant coronary stenoses on angiography [9]. As a consequence, there have been several reports of incidental aortic valve calcification detected during computed tomography examinations with a prevalence of 10–30% [10,11]. However, there have been few reports [11] assessing the relationship between the degree of valvular calcification and the severity of aortic stenosis. We hypothesized that valvular calcification would correlate with the aortic post-valve velocity in patients with aortic stenosis.

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MATERIALS AND METHODS

Subjects

One hundred and fifty-seven patients participated in the study, which was undertaken with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each participant. This is a sub-study of the Scottish Aortic stenosis and Lipid-lowering Therapy, Impact on REgression (SALT-IRE) trial that is evaluating the effect of lipid lowering therapy on the rate of progression of aortic stenosis. Patients with aortic stenosis were approached for inclusion in the trial if they were older than 18 years and had a peak aortic valve velocity of ≥ 2.5 m/s on Doppler echocardiography. Patients were excluded if they were women of child-bearing potential, had active liver disease, were planned to receive or were receiving lipid-lowering therapy, had severe mitral valve disease, aortic regurgitation or planned valve replacement. One patient, with a previous aortic root abscess, was excluded because of extensive aortic root calcification that obscured and prevented assessment of the aortic valve.

All patients underwent both echocardiography and computed tomography within the month before randomization to study therapy (atorvastatin 80 mg daily or placebo). Only pre-intervention baseline data are presented here.

Echocardiography

The echocardiograms were all performed on an ATL-3000 cardiac ultrasound machine [Philips Medical Systems (UK) Limited, Stevenage, UK] using a 3 MHz transducer for M-mode, and two-dimensional imaging with integral pulsed and continuous wave Doppler. The peak instantaneous aortic valve gradient was determined using the modified Bernoulli equation, and the aortic valve area by the continuity equation. Aortic valve calcification was graded using the Rosenhek classification [4]. A single operator blinded to the results of the computed tomogram performed all echocardiographic examinations and analyses.

Computed Tomography

The computed tomography was performed using a multislice helical scanner [Twin II Flash; Philips Medical Systems (UK) Limited, Stevenage, UK]. The region of the aortic valve and coronary arteries was assessed using 2.7 mm slices, with a pitch of 0.7 and an increment of 1.4 mm during held inspiration. Operators blinded to the results of the echocardiogram performed all examinations and analyses. CT scanner quality assurance was performed before each examination with calibration against a standard phantom. Off-line analysis of the cardiac images was conducted using an automated, computerized software program (Picker Cardiac Scoring). This employs a modified Agatston scoring method [12] that uses a threshold of 90 HU to compensate for non-gated imaging. This modification produces comparable sensitivity and specificity to electron beam CT. Calcium scores were individually calculated for the aortic valve, and all three coronary arteries by summing the lesion scores for all sections containing calcium.

Reproducibility

Two unselected random samples of 20 patients each were taken from the study population. Subjects underwent repeated computed tomography or echocardiography within 4 weeks of the first examination and before administration of the study medication.

Data Analysis and Statistics

Data are expressed as mean ± standard deviation of the mean (SD). The calcium scores were not normally distributed and are expressed as median with interquartile ranges. After calibration with the study phantom, the aortic valve and coronary artery calcium volume scores are expressed as arbitrary units (AU). Reproducibility was assessed by the method of Bland and Altman [13], and expressed as the mean of the differences and the coefficient of repeatability (twice the standard deviation of the differences). As the difference of the two measures was proportional to their mean, the data for the aortic valve calcium score underwent logarithmic transformation [13]. Data were compared using regression analysis and analysis of variance (ANOVA) using StatView version 5.0.1 (SAS Institute Inc., Cary, NC, USA). Where ANOVA demonstrated significant differences in responses, post-hoc comparisons were made using the Fisher's protected least squares difference (PLSD) test (StatView version 5.0.1). Statistical significance was taken at the 5% level.

RESULTS

Patient characteristics are listed in Table 1. In keeping with the study population, patients were predominantly male, elderly and had haemodynamically significant aortic stenosis. Both echocardiography and computed tomography showed excellent reproducibility (Table 2).

Table 1 – Baseline subject characteristics

Number	157
Age (years)	68 ± 11
Sex (male)	71%
Bicuspid aortic valve	5
Atrial fibrillation	11
Echocardiogram	
Pre-valve velocity (m/s)	1.08 ± 0.22
Post-valve velocity (m/s)	3.45 ± 0.66
Peak gradient (mmHg)	49 ± 19
Mean gradient (mmHg)	27 ± 11
Valve area (cm^2)	1.02 ± 0.40
Computed tomogram*	
Aortic valve (AU)	5858 (1555–14596)
Coronary artery (AU)	
LAD	97 (0–603)
Circumflex	0 (0–36)
Right	0 (0–0)
Total	121 (0–731)

Mean ± SD; LAD, left anterior descending. AU, arbitrary units.
* Median (interquartile range).

All but two patients had significant aortic valve calcification on computed tomography (Fig. 1). The median aortic valve calcium score was 5858 AU. The majority of patients (107/157) had detectable coronary artery calcification that predominantly affected the left anterior descending coronary artery. There was no correlation between the magnitude of the aortic valve and total coronary calcium scores ($r = 0.04$, $p = 0.61$).

Comparison Between Echocardiography and Computed Tomography

Echocardiographic grade of calcification correlated weakly with the computed tomography aortic valve calcium score ($r = 0.29$, $p < 0.001$) and the peak post-aortic valve velocity ($r = 0.40$, $p < 0.001$). The computed tomography aortic valve calcium score correlated strongly with the post-valve velocity ($r = 0.54$, $p < 0.0001$: $y = 0.00004x + 3.09$; Fig. 2) and the mean ($r = 0.54$, $p < 0.0001$; $y = 0.0008x + 20.7$) and peak gradient ($r = 0.54$, $p < 0.0001$: $y = 0.0013x + 39.1$) of the aortic valve, but only weakly correlated with the aortic valve area ($r = 0.20$, $p = 0.01$).

Stratifying the patients according to the quintiles of calcification demonstrated a progressive increase in the mean peak post-aortic valve velocity (Fig. 3). All patients with severe aortic valve stenosis (post-valve velocity >4 m/s) had an aortic valve calcium score of >3700 AU. This threshold gives a sensitivity of 100% and specificity of 50% that translates into a negative predictive value of 100% and a positive predictive value of 39% for the detection of severe aortic stenosis. A threshold of 6000 AU gives a sensitivity of 90% and specificity of 66% giving a negative predictive value of 95% and a positive predictive value of 45%.

DISCUSSION

In patients with aortic stenosis, we have demonstrated a close association between the degree of aortic valve calcification and the haemodynamic severity of aortic stenosis. In particular, the presence of severe and potentially critical aortic stenosis is associated with heavy calcification. We suggest that patients found to have incidental aortic valve calcification on computed tomography require further cardiological assessment for aortic stenosis, especially when there is heavy calcification.

This is the first study to compare aortic valve calcium scores with echocardiogram-derived measures of valvular gradients in a large number of patients with aortic stenosis. One previous study of 19 patients also suggested that there may be an association between the severity of aortic stenosis and the valvular calcium score [14]. We have studied a larger population with sufficient power to demonstrate a marked correlation between these parameters. However, because of the selected study population, these findings should only be cautiously extrapolated to aortic valve calcification identified during general population screening or as an incidental finding. A recent retrospective study suggested a 20% incidence of aortic valve calcification in over 2000 patients attending for detection of coronary calcification [14]. One retrospective study of 109 such patients who had undergone both computed tomography and echocardiography, reported a 30% prevalence of aortic valve calcification in which aortic stenosis was documented in 15% [11]. In the absence of aortic valve calcification, none of the patients had significant aortic valve stenosis. In the current study, only two patients (1%) had no detectable valvular calcification suggesting an excellent negative predictive value. Our study findings additionally suggest that the likelihood of significant valvular stenosis increases with the severity of calcification.

Echocardiography is the mainstay of clinical monitoring for aortic valve stenosis but provides only a subjective and semi-quantitative measure of aortic valve calcification. Computed tomography provides a more accurate method of quantifying calcium that more closely correlates with the aortic valve gradient than echocardiography-derived measures of calcification. It may be useful to quantify more accurately the degree of calcification given that it is the strongest independent risk factor for disease progression and an adverse clinical outcome [4]. Further prospective studies are now needed to assess whether the degree of calcification [15] provides useful additional clinical information that would help guide patient management. Indeed, it has been suggested that patients with severe aortic stenosis and marked calcification should undergo aortic valve replacement even in the absence of symptoms [4].

Aortic valve calcification is associated with an increased cardiovascular mortality [16]. The underlying pathogenetic process appears to share many of the features and risk factors for atherosclerosis [2] including hypercholesterolaemia [17,18] that is associated with a more rapid progression of aortic valve calcification [15]. There are several ongoing studies, including the SALTIRE trial, that are assessing the impact of lipid-lowering therapy on the rate of progression of aortic stenosis. Given that statin use is associated with halting the progression of coronary calcification [19], the present study indicates that multislice helical computed tomography is a valuable method

Table 2 – Reproducibility of echocardiographic and computed tomographic assessments of the aortic valve ($n = 20$)

	Mean	Mean of differences	Standard deviation of differences	Coefficient of repeatability
Echocardiogram				
Post-valve velocity (m/s)	3.20 ± 0.11	0.0	0.16	0.32
Peak gradient (mmHg)	41.7 ± 3.0	0.0	4.1	8.2
Mean gradient (mmHg)	21.6 ± 1.8	0.2	3.8	7.6
Valve Area (cm^2)	1.17 ± 0.10	0.06	0.39	0.78
Computed tomography*				
Valve calcium score (pAU)	3.86 ± 0.49	0.01	0.04	0.07

* Aortic valve calcium score has undergone logarithmic transformation.

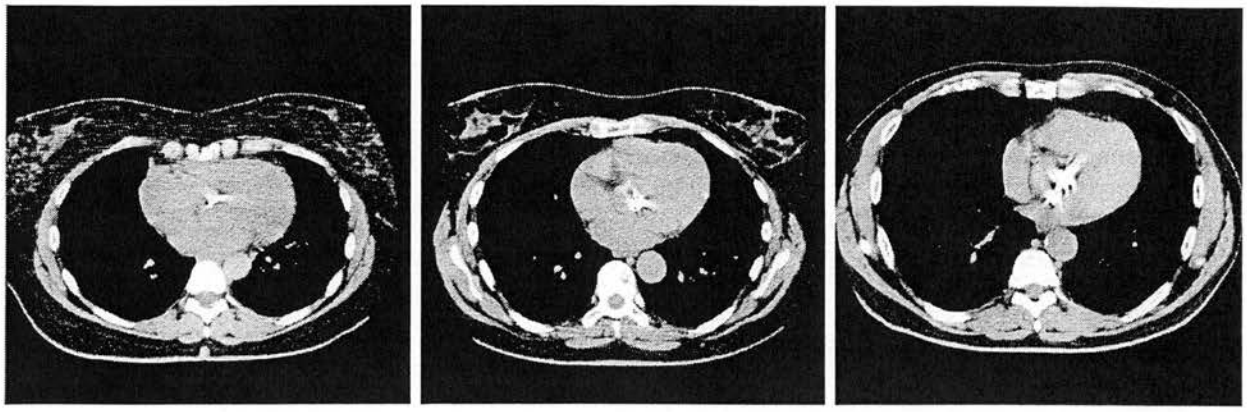

Fig. 1 – Representative computed tomograms showing mild, moderate and severe calcification of the aortic valve.

of assessing aortic valve calcification and disease progression in such intervention trials. Indeed, one preliminary observational study has suggested that statin use is associated with a lower rate of progression of aortic valve calcification [20].

Using our methodology, we have found a close correlation between echocardiographic measures of aortic stenosis and aortic valve calcium scores measured by multislice helical computed tomography. The applicability of our findings to other CT machines with differing specifications, such as 2, 4 or 16 slice acquisitions, or imaging parameters, such as slice thickness and pitch, is unknown. However, there is a high degree of agreement between different machines and coronary calcium scores [21], and we believe that our findings will be applicable to other computed tomography equipment. The reference ranges of the aortic valve calcium scores are likely to be dependent on the imaging protocol and CT equipment used. However, broadly speaking, poorly defined or diffuse segments of calcium usually represent a minor aortic valve gradient. In contrast, coalescent calcium centred on the aortic valve is likely to represent moderate stenosis whereas very heavy calcification almost invariably represents a significant degree of valvular stenosis (Fig. 1).

In conclusion, calcification of the aortic valve is closely associated with the severity of aortic stenosis and heavy

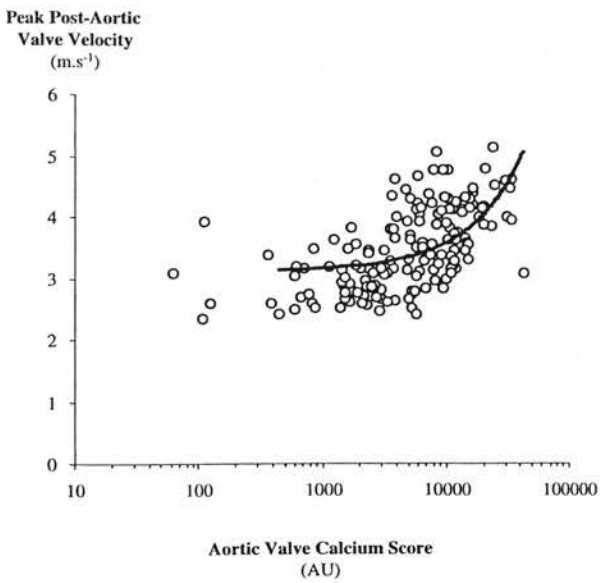

Fig. 2 – Correlation of aortic valve calcification and peak post-aortic valve velocity ($r = 0.54$, $p < 0.001$).

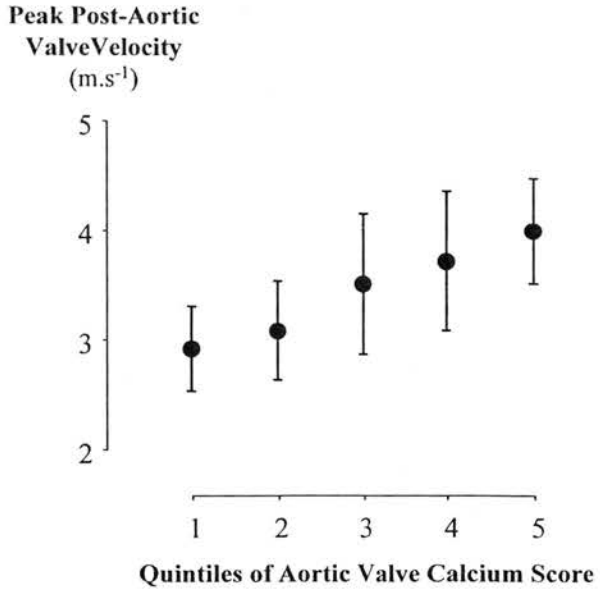

Fig. 3 – Mean (± SD) post-aortic valve velocity in the quintiles of aortic valve calcification. ANOVA $p < 0.001$. Fisher's PLSD test $p \leq 0.03$ for all comparisons between the individual quintiles except quintile 1 *vs* quintile 2, and quintile 3 versus quintile 4.

calcification suggests the presence of severe aortic stenosis that requires urgent cardiological assessment. Patients with lesser degrees of aortic valve calcification should be screened for aortic stenosis and monitored for disease progression.

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REVIEW

Calcific aortic stenosis: same old story?

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Abstract

Calcific aortic stenosis is the commonest adult valvular heart condition seen in the western world. Its prevalence is continuing to rise, with predominance in older patients who are frequently undergoing successful aortic valve replacement. This review discusses the natural history of calcific aortic stenosis, highlights recent insights into its pathogenesis, and outlines current medical and surgical management. The potential role of novel therapeutic interventional strategies is discussed.

Keywords: *aortic stenosis, aetiology, pathogenesis, management, medical therapy, elderly*

Introduction

Aortic stenosis is the commonest adult heart valve condition seen in the western world. Over the last 30–50 years, its diagnosis and management have been revolutionised by the development of invasive (cardiac catheterisation) and non-invasive (echocardiography) haemodynamic assessments as well as potentially curative cardiac surgery. Recent insights have been made into the pathogenesis of calcific aortic stenosis, resulting in speculation that the disease mimics atherosclerosis and progression could be delayed or prevented by the use of lipid lowering therapy. This exciting concept is currently under investigation in a number of centres and, if successful, may potentially reduce the need for aortic valve surgery.

Epidemiology

Calcific aortic stenosis was first documented in 1904 [1] and at that time was regarded as uncommon. In the 19th century, calcific aortic stenosis was not recognised as a clinical entity since pathological studies revealed only cusp thickening and sclerosis [2]. As a result, aortic valve sclerosis (thickening without stenosis) and aortic valve stenosis were regarded as different pathological conditions for many decades. Recent evidence, however, suggests that they represent different stages of the same disease process [3–5]: sclerosis arising from the development of valvular calcific lesions that progress slowly over several decades before ultimately causing aortic stenosis [6]. The current prominence of calcific aortic valve disease is likely to represent increased human longevity associated with the declining prevalence of rheumatic fever.

Aortic valve sclerosis is present in 20–30% of individuals over 65 years and 48% over 85 years [7], and aortic stenosis in 2% and 4%, respectively [3, 7, 8]. Calcific sclerosis and valvular stenosis occur in patients with both a normal tricuspid aortic valve as well as in those with a bicuspid valve. The prevalence of bicuspid aortic valves is difficult to determine but is estimated to affect 1–2% of the general population [9]. Up to 70% of patients with a bicuspid aortic valve develop valvular stenosis [9] and will require aortic valve replacement 1–2 decades earlier in life (5th–6th decade) than in those with a tricuspid aortic valve.

Natural history

Prior to the introduction of haemodynamic assessment and cardiac surgery, the natural history of aortic stenosis was described by its clinical presentation. Calcific aortic stenosis is a gradually progressive disease, characterised by a long asymptomatic phase lasting several decades, followed by a shorter symptomatic phase usually associated with severe narrowing of the aortic valve orifice.

The outlook for patients with asymptomatic aortic stenosis is generally good and closely matches that of life table estimates for age- and sex-matched controls [10]. A striking feature of aortic stenosis is that the prognosis changes dramatically with the onset of symptoms in association with severe outflow obstruction: a 2-year survival rate of 50%. Although few studies specifically assessed the influence of age, patients over the age of 70 have a worse prognosis with 2- and 3-year survival rates of 37% and 25%, respectively [11]. The prognosis also depends upon the clinical presentation with a mean survival of 3 years for those presenting with angina

and syncope, 2 years with the onset of breathlessness, and as little as 1 year in those who develop overt left ventricular failure [12, 13].

Other cardiovascular events

Despite the favourable outlook in those patients with mild asymptomatic disease, there is an increased risk of cardiovascular events unrelated to the aortic valve disease. Otto and colleagues demonstrated that, in patients with aortic sclerosis, there is a 50% increased risk of myocardial infarction and cardiovascular death even in the absence of significant outflow tract obstruction [7]. The Helsinki Aging Study also suggested that patients with moderate to severe aortic stenosis had higher all cause and cardiovascular mortality irrespective of associated symptoms. In particular, a higher rate of stroke related death was noted although the majority of these patients had atrial fibrillation [**14**].

Pathology of calcific aortic stenosis

For many decades, calcific aortic stenosis has been attributed to prolonged 'wear and tear' and age-associated valvular degeneration. Contrary to this supposition, however, is the absence of aortic valve calcification or stenosis on echocardiography in a third of individuals over the age of 80 [**8**]. Recent evidence suggests that calcific aortic stenosis may result from an active inflammatory process involving biochemical, humoral and genetic factors.

Histology

Normal aortic valve leaflets are macroscopically smooth, thin and opalescent, with clearly defined tissue layers at a microscopic level and very few cells [15]. Increasing age gives rise to non-specific thickening of the tips of the valve leaflets, with an increase in the number of adipose cells and thinning of tissue layers [**16**]. In calcific aortic stenosis, there is characteristic leaflet thickening, with irregular nodular masses on the aortic aspect of the valve. Microscopic assessment of both mild and severely affected valves reveals endothelial and basement membrane disruption, with underlying subendothelial thickening. The lesion itself contains disorganised collagen fibres, chronic inflammatory cells, lipoproteins, lipid, extracellular bone matrix proteins and bone mineral [15, **16**].

Pathogenesis

The histological features described closely resemble those seen in atherosclerosis and are strongly suggestive of chronic inflammation. In calcific aortic stenosis, the factors initiating the inflammatory process have not been identified but mechanical injury to the endothelium is thought to pave the way for subsequent inflammation. This concept is supported by the pattern of aortic valve cusp involvement that corresponds to areas of low shear and high tensile stress: namely the aortic surface of the leaflets and predilection for the non-coronary cusp [17–20]. Congenitally bicuspid aortic valves are less efficient than tricuspid valves at distributing mechanical stress and this may account for the more rapid development of stenosis [21].

Role of lipids

Endothelial injury or disruption may allow circulating lipids to enter the valvular interstitial tissue [**22**] and accumulate in areas of calcification and inflammation [**22, 23**]. The lipoproteins implicated in atherogenesis, including low-density lipoprotein (LDL) and lipoprotein (a), are present in early aortic valve lesions [**22**] and undergo oxidative modification [**23**]. These oxidised lipoproteins are highly cytotoxic [24] and capable of stimulating inflammatory activity [25, 26] and mineralisation [27–**29**].

Inflammation

Both macrophages and activated T lymphocytes are present in the early and advanced lesions of congenitally bicuspid [30] and tricuspid aortic valves [15, **16**]. Migration of these effector inflammatory cells appears to be mediated through increased endothelial expression of cellular adhesion molecules such as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [31, 32]. Once recruited into the subendothelium, the inflammatory cells release enzymes, such as matrix metalloproteinases, that cause degradation of collagen, elastin and proteoglycans within the aortic valve cusps [33].

Calcification

Mineralisation is a characteristic of both atherosclerotic and aortic valve lesions, and arises in close proximity to areas of inflammation. It is a prominent feature in calcific aortic stenosis and has been demonstrated in early [**16**] as well as advanced lesions [**34**]. Surgically excised valves have even revealed areas of mature lamellar bone, haemopoietic marrow and bone remodelling [**34**]. Several features suggest the presence of an active highly regulated process closely resembling developmental bone formation [35, **36**].

The initiation of mineralisation (nucleation) may be stimulated by the presence of cellular degradation products following apoptosis [37] or by the presence of oxidised lipids [**23**, 34]. *In vitro* studies of cultured explants of stenotic valves have identified cells with osteoblastic characteristics capable of phenotypic differentiation and spontaneous calcification [38]. Their origin is unknown but they may be derived from a pool of circulating immature pluripotent mesenchymal cells [39]. These osteogenic cells or 'calcifying valvular cells' express and produce a variety of regulatory bone matrix proteins including osteopontin [40, 41] and bone morphogenetic protein [**34**].

Similarities and differences with atherosclerosis

Although the similarities with atherosclerosis were recognised as long ago as 1917 [42], they were largely disregarded until recently [43–**45**]. The histological studies described above have highlighted the common features but also confirmed differences in the cellular and mineral components of the two lesions.

Smooth muscle proliferation and lipid-laden macrophages (or foam cells) are prominent features of vascular atheroma but are virtually absent in stenotic aortic valves. In

addition, mineralisation is an earlier and more extensive feature of aortic valve lesions compared with atherosclerosis [16]. These differences may, in part, explain why only 40% of patients with severe aortic stenosis have significant coronary artery disease [46–50] and why the majority of patients with coronary artery disease do not have aortic stenosis. As the underlying pathology for the two conditions appears to be similar, it is likely that other unknown factors influence the development of valvular as opposed to vascular lesions [51].

Clinical presentation

Patients present with either an incidentally noted asymptomatic systolic murmur or with symptoms of severe disease including angina, exertional syncope, breathlessness, and reduced exercise tolerance or lethargy. In simple terms, progressive obstruction to outflow results in a gradual rise in left ventricular pressures, left ventricular hypertrophy, and diastolic dysfunction. Once the degree of stenosis is severe, further small decreases in aortic valve area result in large changes in the pressure gradient across the valve. Symptoms and decompensation arise due to the development of inadequate cardiac reserve, myocardial oxygen demand mismatch or pressure overload of the left ventricle. Symptoms rarely occur unless the degree of stenosis is of at least moderate severity (with an aortic valve area of less than 1.0 cm^2) but patients may remain asymptomatic for long periods with even very severe stenosis [46].

Clinical risk factors

In keeping with the apparent parallels with atherosclerosis, calcific aortic stenosis is associated with coronary artery disease [48, 50] and many of its risk factors (Table 1) [3]. Calcific aortic stenosis is also seen in association with severe homozygous familial hypercholesterolaemia, and its development appears to be influenced by the length of exposure to elevated serum cholesterol concentrations [52]. Interestingly, aggressive lipid lowering therapy with plasmapheresis has been reported to regress aortic stenosis in such patients [53]. Milder forms of hypercholesterolaemia have also been associated with calcific aortic stenosis [54, 55, 56], particularly in patients with non-rheumatic tricuspid valves [54].

Table 1. Risk factors for calcific aortic stenosis

Clinical	Biochemical
Age	Hyperlipidaemia (LDL and Lp (a))
Male sex	Hypercalcaemia
Smoking	Elevated serum creatinine
Hypertension	
Diabetes mellitus	
Coronary artery disease	
Chronic renal failure	
Paget's disease	
Hyperparathyroidism	

LDL = Low-density lipoprotein; Lp (a) = Lipoprotein a.

Conditions affecting calcium metabolism, such as chronic renal impairment with secondary hyperparathyroidsim [57–59] and advanced Paget's disease [60], predispose individuals to aortic valve calcification and accelerated stenosis. Such patients also tend to have diffuse cardiac calcification affecting the mitral valve, myocardium and conducting system.

A number of twin studies and case reports suggest that hereditary factors may influence the development of calcific aortic valve stenosis [61, 62]. There has been a single report of a genetic association between aortic stenosis and a vitamin D receptor polymorphism [63] but this finding has yet to be confirmed.

Investigations

The assessment of valvular stenosis and monitoring of disease progression has only been possible over the last five decades using cardiac catheterisation, echocardiography and more recently magnetic resonance (MR) imaging and computed tomography (CT). Magnetic resonance may have some advantages over echocardiography in assessment of stenosis severity [64], but its availability is limited and measurements are time consuming to perform. Although currently limited to clinical research, CT has recently been validated as an accurate means of quantifying aortic valve calcification, a measure that correlates well with the severity of stenosis estimated by echocardiography [65]. Echocardiography remains the current gold standard for monitoring of disease progression and left ventricular function in patients with aortic stenosis.

The severity of aortic valve stenosis is assessed using both two-dimensional and Doppler echocardiography (Table 2). Narrowing of the aortic valve orifice results in acceleration of blood flow across the valve. Using spectral Doppler, the velocity of blood passing through the left ventricular outflow tract (pre-valve) and aortic valve orifice (post-valve) can be measured and is usually expressed in metres per second. The peak instantaneous pressure gradient across the aortic valve has a simple relationship with the peak post-valve velocity and is described as four times the square of the velocity (modified Bernoulli equation). For example, a peak post-valve velocity of 4 m/s gives an instantaneous pressure gradient of $4 \times 4^2 = 64$ mmHg. Where there are concerns that impaired left ventricular function limits the ability to generate an adequate pressure gradient across the valve, measurement of the aortic valve area may

Table 2. Echocardiographic measures of severity of aortic stenosis (AS)

	Normal	Mild AS	Moderate AS	Severe AS
Peak post-valve velocity (m/s)	0.9–1.8	2.5–3.0	3.0–4.0	>4.0
Peak gradient (mmHg)	<25	25–36	36–64	>64
Aortic valve area (cm^2)	2.0–3.5	1.0–2.0	0.5–1.0	<0.5

need to be made using direct planimetry or indirectly using the continuity equation. On occasions, dobutamine stress echocardiography may be used as method of distinguishing true aortic stenosis causing left ventricular dysfunction from aortic pseudostenosis where the impairment of the left ventricle causes poor excursion of the aortic valve cusps giving the impression of stenotic valvular restriction.

Disease progression

Echocardiography provides the most accurate evaluation of disease progression, which can be unpredictable and extremely variable. Some individuals show little or no evidence of deterioration over time, yet others progress rapidly from mild to severe stenosis within a few years.

In patients with aortic valve sclerosis, progression to stenosis (arbitrarily defined as a peak post-valve velocity ≥2.5 m/s, or peak gradient ≥25 mmHg) is a relatively slow process with mean increases in peak post valve velocity and peak gradient of 0.07 m/s and 1.4 mmHg per year, respectively [**66**]. However, once the valve is classified as stenotic, disease progression is more rapid with average increases of 0.3 m/s and 7–8 mmHg per year, corresponding to a decrease in aortic valve area of 0.1 cm^2 per year [67–**71**].

Predictors of progression and clinical outcome

Disease progression and clinical outcome have been linked to many of the risk factors for calcific aortic stenosis, including age, male sex, hyperlipidaemia, hypertension, diabetes mellitus, smoking, hypercalcaemia and chronic renal impairment [69, 72, **73**–75]. However, much of the evidence is conflicting and limited by the retrospective nature of the studies. The most consistent and strongest predictors of disease progression are severity of stenosis at baseline [**71**] and degree of valvular calcification [72, 76, **77**]. The more severe the stenosis at baseline and the more heavily calcified the valve, the faster the rate of progression. Clinical outcome is also influenced by the degree of valvular calcification, with nearly 80% of patients with moderate to severe calcification who progress rapidly (>0.3 m/s/yr) either dying or undergoing aortic valve replacement within 2 years [**77**].

Management of calcific aortic stenosis

At the present time, there is no known therapy that can slow or reverse disease progression in patients with calcific aortic stenosis. Current management includes monitoring disease progression, and ensuring patient awareness of the need for antibiotic prophylaxis against infective endocarditis. For those patients with severe symptomatic disease, the therapeutic options include conventional medical therapy for symptom control and aortic valve replacement.

General advice

All patients should be advised of the need for antibiotic prophylaxis against endocarditis for dental and other invasive procedures. Patients with moderate or severe disease should be advised to avoid strenuous physical exercise and competitive sport, and to report promptly the onset of symptoms.

Monitoring of disease progression

Since disease progression is so unpredictable, the majority of patients should be reviewed regularly to monitor changes in stenosis severity and watch for the onset of symptoms. As a rule of thumb, asymptomatic patients with mild to moderate stenosis require review and echocardiography every 1–2 years, and those with moderate to severe stenosis every 6–12 months. Patients developing symptoms between appointments should be reviewed immediately.

Asymptomatic severe aortic stenosis

One contentious area of management is determining the optimal timing for aortic valve replacement. It is universally accepted that surgery is indicated as soon as symptoms appear in patients with severe stenosis. Although many cardiologists are loath to refer patients without symptoms for valve surgery, there are some who feel uncomfortable managing patients with severe asymptomatic valvular stenosis because of the potential risk for sudden cardiac death. However, this is rare and occurs in less than 1% of asymptomatic patients per year [**78**]. The combined risk of aortic valve replacement (2–10% mortality) and prosthesis-related complications (2–3%/year) is thus greater than the risk of sudden cardiac death. 'Watchful waiting' is therefore recommended.

The onset of symptoms in patients with severe stenosis may be subtle and insidious, particularly in the elderly where co-morbidity may mislead or obscure the presentation. For this reason careful history taking for changes in exercise tolerance as well as the classical symptoms of breathlessness, chest pain and syncope is required. In cases where patients may be underplaying symptoms, attributing them to 'old age', or unknowingly avoiding activity that induces symptoms, physician supervised exercise testing may be helpful in both revealing symptoms as well as determining the haemodynamic response to exercise. Patients who develop symptoms during exercise, become hypotensive, manifest marked ST segment changes or develop ventricular arrhythmias are at high risk and should be referred for valve replacement [79–**81**].

Symptomatic severe aortic stenosis

As soon as patients with severe aortic stenosis develop symptoms the treatment of choice is aortic valve replacement because this substantially improves quality of life and prognosis. In those patients declining valve surgery, or the frail elderly in whom major cardiac surgery would be inappropriate, palliation with conventional medical therapy, or in exceptional circumstances, balloon valvotomy are the only alternatives. Percutaneous aortic valve replacement is a promising new technique that is currently under development in highly selected patient populations [82, 83].

Medical therapy

Breathlessness

Patients with evidence of pulmonary congestion may benefit from the judicious use of diuretics, vasodilators and positive inotropic agents such as digoxin. Excessive use of diuretics should be avoided since patients with severe aortic

stenosis often have diastolic dysfunction and depend on an adequate pre-load in order to maintain their cardiac output.

Despite the widespread belief that ACE inhibitors can cause dangerous hypotension in severe aortic stenosis, and are therefore contraindicated, there are little data to support this. From the limited literature available, two small studies demonstrated that first dose hypotension did not occur in patients with severe aortic stenosis, and that cardiac output and symptoms improved substantially [84, 85]. Although further study is required, some patients with heart failure and severe aortic stenosis could benefit from ACE inhibitors provided that they are carefully introduced in a hospital setting. Certainly those patients already established on therapy need not have it withdrawn since this may precipitate the onset of heart failure.

Digoxin can be helpful in the management of heart failure but should only be used in the presence of atrial fibrillation or where there is documented evidence of left ventricular systolic dysfunction. Atrial fibrillation is not well tolerated in the presence of severe stenosis and restoration to sinus rhythm (through DC cardioversion or pharmacological cardioversion using amiodarone) should be attempted wherever possible.

Angina

In those individuals where angina is the predominant symptom, cautious use of beta blockers and nitrates may be of benefit.

Syncope

Patients with syncope or pre-syncope should be further evaluated with a 24-hour cardiac monitor since aortic stenosis is commonly associated with atrioventricular block. There is no specific therapy for syncope unless it is caused by a bradyarrhythmia or tachyarrhythmia, where pacemaker insertion or antiarrhythmic therapy, respectively, should be considered.

Balloon valvotomy

Although balloon valvotomy plays an important role in the management of adolescents and young adults with aortic stenosis, it has largely been abandoned in older patients. The functional improvement obtained is limited, the restenosis and complication rates are high, and the long term outlook poor (<80% survival at 1 year) [**78**, 86]. On rare occasions, balloon valvotomy may play a role in patients with a limited life expectancy for other reasons, or as a bridge to aortic valve replacement in critically ill patients with cardiogenic shock.

Aortic valve replacement

Aortic valve replacement incurs the virtual abolition of symptoms associated with improvements in physical functioning and quality of life, and a dramatic improvement in survival. Operative mortality in middle-aged adults is in the region of 5–8% [**87**, **88**, 89] with 5- and 10-year survival rates of approximately 80% [**87**, 90] and 65%, respectively [**87**], which approaches actuarial survival rates for the general population [**87**].

Factors associated with a higher operative mortality include increasing age [91], the presence of renal impairment, cerebrovascular and peripheral vascular disease [92], the presence of impaired left ventricular function [91], and the need for simultaneous coronary artery bypass grafting [**88**]. Despite the increased operative risk associated with the presence of left ventricular failure, this is not an absolute contra-indication to surgery. Indeed these patients may have the most to gain from valve surgery in terms of improvements in prognosis.

Aortic valve replacement in octogenarians

Successful aortic valve replacement is becoming increasingly common in patients over the age of 80. Despite evidence suggesting that it should be offered to all suitable patients regardless of age, several studies have demonstrated a reluctance to refer older patients for valve surgery [8, 93, 94]. This probably reflects both patient and physician misconceptions of the risks and benefits of operative intervention.

Although operative mortality is higher in octogenarians (nearer 5–15%), these individuals have almost as much to gain as their younger counterparts in terms of improved prognosis (5-year survival being 55–70%). Of perhaps greater importance is that the majority of survivors achieve a significant reduction in symptoms [92, 95, 96, **97**, **98**] associated with a marked improvement in physical functioning and quality of life [**88**, 95, 96, **98**]. Although intensive care [92, **98**] and overall hospital stay [95, **97**, **98**] may be longer, the majority return to their own homes and retain their independence on discharge [92, 95]. However, post-operative complications are more common with a higher incidence particularly of stroke (4%) and acute renal failure (7–10%) [**98**]. In contrast to younger patients, octogenarians are usually offered a bioprosthetic (as opposed to a mechanical) valve, thus reducing the risk of valve thrombosis and anticoagulant associated haemorrhage.

Potential role for HMG CoA reductase inhibitors

Hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitors or statins are now well established in the primary and secondary prevention of coronary artery disease [99, 100]. Several studies have also shown that these drugs can cause regression of coronary artery disease [101] as well as reduce the calcific volume of coronary plaques [102]. Given the clinical association of calcific aortic stenosis with hyperlipidaemia and coronary artery disease, and the striking histological similarities with atheroma, the speculation that statins may have the potential to influence disease progression in aortic stenosis is an intriguing hypothesis [**103**, **104**].

Recent retrospective studies [105–**109**] have demonstrated that statins may delay disease progression in aortic stenosis through their lipid-lowering and anti-inflammatory actions [**109**]. These observational data should be interpreted with caution since none of these studies was randomised, and the statin doses were small. This preliminary evidence has been the rationale for establishing several ongoing randomised controlled trials of statin therapy in patients with aortic stenosis, such as the Scottish Aortic stenosis and

Lipid lowering Therapy, Impact on REgression (SALTIRE) and Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trials.

Conclusion

The need for an alternative to aortic valve surgery is highlighted by the increasing longevity of the population and rising prevalence of aortic stenosis. New therapeutic strategies to limit disease progression are needed in order to delay, and potentially avoid, the need for valve surgery. The outcomes of several ongoing randomised controlled trials investigating the role of lipid-lowering therapy in aortic stenosis are awaited with interest.

Key points

- Aortic stenosis is increasingly common.
- Severe aortic stenosis in the presence of symptoms carries a very poor prognosis.
- Aortic valve replacement dramatically improves survival and quality of life, even in octogenarians.
- Too few older patients are offered aortic valve replacement.
- Lipid-lowering therapy may have a potential role in the prevention of disease progression.

Conflicts of interest declaration

The authors are currently involved in the SALTIRE trial funded by the British Heart Foundation with an additional educational grant award from Pfizer (UK) Limited, as well as the SEAS study which is sponsored by Merck Sharp and Dohme Limited.

Please note

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website (http://www.ageing.oupjournals.org).

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ORIGINAL ARTICLE

A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

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ABSTRACT

BACKGROUND

Calcific aortic stenosis has many characteristics in common with atherosclerosis, including hypercholesterolemia. We hypothesized that intensive lipid-lowering therapy would halt the progression of calcific aortic stenosis or induce its regression.

METHODS

In this double-blind, placebo-controlled trial, patients with calcific aortic stenosis were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. Aortic-valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical computed tomography, respectively. The primary end points were change in aortic-jet velocity and aortic-valve calcium score.

RESULTS

Seventy-seven patients were assigned to atorvastatin and 78 to placebo, with a median follow-up of 25 months (range, 7 to 36). Serum low-density lipoprotein cholesterol concentrations remained at 130±30 mg per deciliter in the placebo group and fell to 63±23 mg per deciliter in the atorvastatin group ($P<0.001$). Increases in aortic-jet velocity were 0.199±0.210 m per second per year in the atorvastatin group and 0.203±0.208 m per second per year in the placebo group ($P=0.95$; adjusted mean difference, 0.002; 95 percent confidence interval, −0.066 to 0.070 m per second per year). Progression in valvular calcification was 22.3±21.0 percent per year in the atorvastatin group, and 21.7±19.8 percent per year in the placebo group ($P=0.93$; ratio of post-treatment aortic-valve calcium score, 0.998; 95 percent confidence interval, 0.947 to 1.050).

CONCLUSIONS

Intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. This study cannot exclude a small reduction in the rate of disease progression or a significant reduction in major clinical end points. Long-term, large-scale, randomized, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis.

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In the Western world, calcific aortic stenosis is the most common form of valvular heart disease, and its incidence increases with age such that 3 percent of adults over 75 years of age have aortic stenosis.[1] It is a gradually progressive disease, characterized by a long asymptomatic phase, lasting several decades, followed by a shorter symptomatic phase associated with severe narrowing of the orifice of the aortic valve. Once symptoms occur, the prognosis is poor and surgery is usually mandated. Calcific aortic stenosis is now the leading indication for valve replacement in North America and Europe. However, there are currently no effective disease-modifying treatments, and the possibility of halting the disease process would represent a therapeutic advance.

Calcific aortic stenosis is mediated by a chronic inflammatory disease process that has many similarities with atherosclerosis and includes inflammatory-cell infiltrates, lipoproteins, lipids, extracellular-bone-matrix proteins, and bone mineral.[2-5] Consistent with these observations, clinical studies have revealed a strong association with coronary artery disease[6,7] and many of its risk factors, including hypercholesterolemia.[1] Disease progression in aortic stenosis is variable and influenced by several factors, including the degree of stenosis,[8] valvular calcification,[9-11] and hypercholesterolemia.[12,13] Indeed, calcific aortic stenosis is a feature of severe homozygous familial hypercholesterolemia,[14] and intensive lipid-lowering therapy with plasmapheresis can reverse valvular stenosis in patients with this disease.[15]

The use of hydroxymethylglutaryl–coenzyme A reductase inhibitors, or statins, is an established treatment for the primary and secondary prevention of coronary artery disease.[16,17] Several studies have shown that these drugs can halt the progression of coronary artery disease[18-20] and reduce coronary calcification.[21-23] Given the clinical association with hypercholesterolemia and coronary artery disease, and the histologic similarities with atheroma, it has been suggested that statin therapy may halt the progression, or even induce regression, of calcific aortic stenosis. This hypothesis is supported by numerous retrospective observational studies[24-29] showing that concomitant statin therapy was associated with a delay in disease progression, demonstrated by a reduction of 0.30 m per second per year in the rate of change in aortic-jet velocity, and of 30 percent per year in valvular calcification.

The aim of the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) was to establish whether intensive lipid-lowering therapy with 80 mg of atorvastatin daily would halt the progression or induce regression of the aortic-jet velocity on Doppler echocardiography, and of the aortic-valve calcium score on computed tomography (CT), in patients with calcific aortic stenosis.

METHODS

PATIENTS

Patients older than 18 years of age with calcific aortic stenosis, an aortic-jet velocity of at least 2.5 m per second, and aortic-valve calcification on echocardiography[11] were eligible for inclusion. Exclusion criteria were child-bearing potential without contraception, active or chronic liver disease, a history of alcohol or drug abuse, severe mitral-valve stenosis (mitral-valve area, <1 cm^2), severe mitral or aortic regurgitation,[30] left ventricular dysfunction (ejection fraction, <35 percent), a planned aortic-valve replacement, intolerance of statins, statin therapy or a potential benefit from statin therapy (according to the treating physician), a baseline serum total cholesterol concentration of less than 150 mg per deciliter (4.0 mmol per liter), and presence of a permanent pacemaker or cardiodefibrillator. Of the patients screened, 455 were eligible for inclusion, 173 agreed to participate, and 155 ultimately underwent randomization.

STUDY PROTOCOL

Between March 2001 and April 2002, the blinded study coordinator randomly assigned eligible patients by the minimization technique[31] with the use of a dedicated, locked computer program (Edinburgh University) incorporating the following eight variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, aortic-jet velocity, and aortic-valve calcium score. Patients were assigned to either 80 mg of atorvastatin (Lipitor, Pfizer) or matched placebo as a single daily dose. Numbered containers were used.

Patients were assessed at baseline, two months, and six months and every six months thereafter for a minimum of two years. Clinical evaluation included assessment of functional status and adverse events, and the biochemical analysis of blood. Echocardiography and CT were performed at baseline, at each annual visit, and before withdrawal from the study. Patients who underwent randomization and who were subsequently started on open-

label statin therapy by their attending physician were immediately scanned and withdrawn from the study.

Drs. Cowell, Reid, Northridge, and Bloomfield collected the data; Drs. Newby, Northridge, and Boon designed the study and vouch for the data and the analysis; Dr. Prescott analyzed the data; and all investigators participated in writing the article. The drug and the placebo were provided by Pfizer, who had no other input into the study. The investigation conformed to the Declaration of Helsinki and was approved by all regional ethics committees. All patients gave written informed consent.

ECHOCARDIOGRAPHY

Assessment of valvular stenosis was determined by a single dedicated research ultrasonographer. Patients were studied with the use of a 3-MHz transducer for M-mode (single-dimensional) and pulsed and continuous-wave Doppler scanning. All measurements were determined online, averaged from three cardiac cycles (five cycles if the patient was in atrial fibrillation), and recorded onto super-VHS videotape and optical disk according to a standard protocol.

Peak and mean aortic-valve pressure gradients were calculated with the Bernoulli equation, and aortic-valve area was calculated with the continuity equation. The severity of aortic stenosis was determined with echocardiography according to the following standard guidelines: normal is defined by a peak velocity of 1.0 to 2.0 m per second, peak and mean gradients of 0 mm Hg, and a valve area of greater than 2.0 cm^2; mild by a peak velocity of 2.1 to 3.0 m per second, a peak gradient of 16 to 35 mm Hg, a mean gradient of less than 15 mm Hg, and a valve area of 2.0 to 1.3 cm^2; moderate by a peak velocity of 3.1 to 4.0 m per second, a peak gradient of 36 to 64 mm Hg, a mean gradient of 15 to 50 mm Hg, and a valve area of 1.2 to 0.8 cm^2; and severe by a peak velocity of greater than 4.0 m per second, a peak gradient of greater than 64 mm Hg, a mean gradient of greater than 50 mm Hg, and a valve area of less than 0.8 cm^2.

COMPUTED TOMOGRAPHY

CT was performed by a single operator with the use of a double-helix scanner (Twin II Flash, Philips Medical Systems) calibrated against a standard phantom. The region of the aortic valve was scanned with a spiral CT with the use of 2.7-mm slices, a pitch of 0.7, and an increment of 1.4 mm during inspiratory breath-holding sessions. All images were analyzed by a single operator with the use of automated computerized software (Picker Cardiac Scoring), involving a modified Agatston scoring method[32] with a threshold of 90 Hounsfield units to compensate for nongated imaging.

Reproducibility of echocardiography and CT assessments was determined in two subsets of 20 patients, as described elsewhere.[33] Coefficients of reproducibility[34] for aortic-jet velocity and aortic-valve calcium score were 0.32 m per second and 0.07 log arbitrary units (AU), respectively.[33]

STATISTICAL ANALYSIS

The two primary end points were progression of stenosis, determined according to changes in aortic-jet velocity on Doppler echocardiography, and progression of valvular calcification, as measured by CT. Secondary end points were a composite of clinical end points (death from cardiovascular causes, aortic-valve replacement, or hospitalization attributable to severe aortic stenosis), aortic-valve replacement, death from any cause, hospitalization for any cause, and hospitalization for cardiovascular causes. On the basis of standard deviations of 0.32 m per second per year[8,29,35] and 1100 AU per year,[32] we calculated that the planned sample size of 75 patients per group would give the study a power of 80 percent at a 5 percent significance level to detect a difference in the primary end points of 0.15 m per second per year in aortic-jet velocity and 500 AU per year in aortic-valve calcium score. These differences are equivalent to a reduction of more than 30 percent in the rate of progression of aortic stenosis. This would exclude a clinically significant effect in the majority of older patients with established disease, although a smaller effect may be clinically relevant in younger patients with mild aortic stenosis.

The data-monitoring committee conducted two interim assessments of safety and an interim assessment of efficacy one year after enrollment began. The trial was to be terminated early in the event of a negative effect of treatment (i.e., $P<0.05$) or a strong benefit of treatment (i.e., $P<0.001$). On the recommendation of the data-monitoring committee, the trial continued until the study was completed.

Analyses were performed using SPSS software, version 12.0, and SAS software, version 8e. Intention-to-treat analyses were used for all clinical outcome variables. Disease progression was deter-

Table 1. **Baseline Characteristics of the Patients.***

Characteristic	Atorvastatin (N=77)	Placebo (N=78)
Age — yr	68±11	68±10
Male sex — %	68	72
Hypertension — no.	48	54
Hyperlipidemia — no.	8	5
Diabetes mellitus — no.	3	4
Current smoker — no.	21	22
Coronary heart disease — no.	18	21
Cerebrovascular disease — no.	9	11
Peripheral vascular disease — no.	5	13
Drug history — no.		
Aspirin	43	40
ACE inhibitor	12	14
Beta-blocker	21	27
Warfarin	8	12
Height — cm	168±9	169±8
Weight — kg	79±15	80±15
Heart rate — bpm	68±11	66±12
Systolic blood pressure — mm Hg	144±18	144±21
Diastolic blood pressure — mm Hg	82±10	81±12
Biochemistry†		
Total cholesterol — mg/dl	220±38	217±34
LDL cholesterol — mg/dl	137±34	133±30
Cholesterol:HDL ratio	4.1±1.1	4.1±1.4
Urea — mg/dl	38±13	43±13
Creatinine — mg/dl	1.07±0.25	1.08±0.26
Glucose — mg/dl	91±19	95±21
Sinus rhythm — %	94	92
Atrial fibrillation — %	6	8
Romhilt–Estes score — median (interquartile range)	1 (0–3)	2 (1–4)
Tricuspid aortic valve — %	96	97
Bicuspid aortic valve — %	4	3
Aortic-jet velocity — m/sec	3.39±0.62	3.45±0.67
Peak gradient — mm Hg	47.8±17.4	49.5±19.5
Aortic-valve area — cm^2	1.03±0.4	1.02±0.41
Aortic-valve calcium score — median AU (interquartile range)	5424 (2750–9689)	6221 (3037–9575)
Log aortic-valve calcium score — log AU	3.7±0.5	3.7±0.6

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, LDL low-density lipoprotein, HDL high-density lipoprotein, and AU arbitrary units.

† To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for urea to millimoles per liter, multiply by 0.357. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for glucose to millimoles per liter, multiply by 0.05551.

mined primarily by dividing the change between the baseline and final scans by the duration of follow-up. Treatment comparisons for the continuous outcome variables were based on an analysis of covariance, with the prerandomization level of a variable used as a covariate. In a confirmatory analysis of the primary end points, random-coefficient models were fitted to incorporate all observations.[36] In the subgroup analyses, interaction terms between treatment and subgroup have been added to a model incorporating prerandomization level, treatment, and subgroup to identify factors that were associated with a differential treatment effect within subgroups. Categorical variables have been analyzed using Fisher's exact test. Two-tailed tests were used throughout. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Seventy-seven patients were assigned to atorvastatin and 78 to placebo, with a median follow-up of 25 months (range, 7 to 36). As a consequence of minimization, baseline characteristics were well matched (Table 1). Mean aortic-jet velocity was 3.43±0.64 m per second (range, 2.5 to 5.0), and the median aortic-valve calcium score was 5920 AU (interquartile range, 2485 to 14,231). Of the 155 patients, 119 had mild-to-moderate aortic stenosis (aortic-jet velocity, 2.5 to 3.9 m per second), and 36 had severe stenosis (aortic-jet velocity, ≥4.0 m per second).

SERUM CHOLESTEROL CONCENTRATIONS

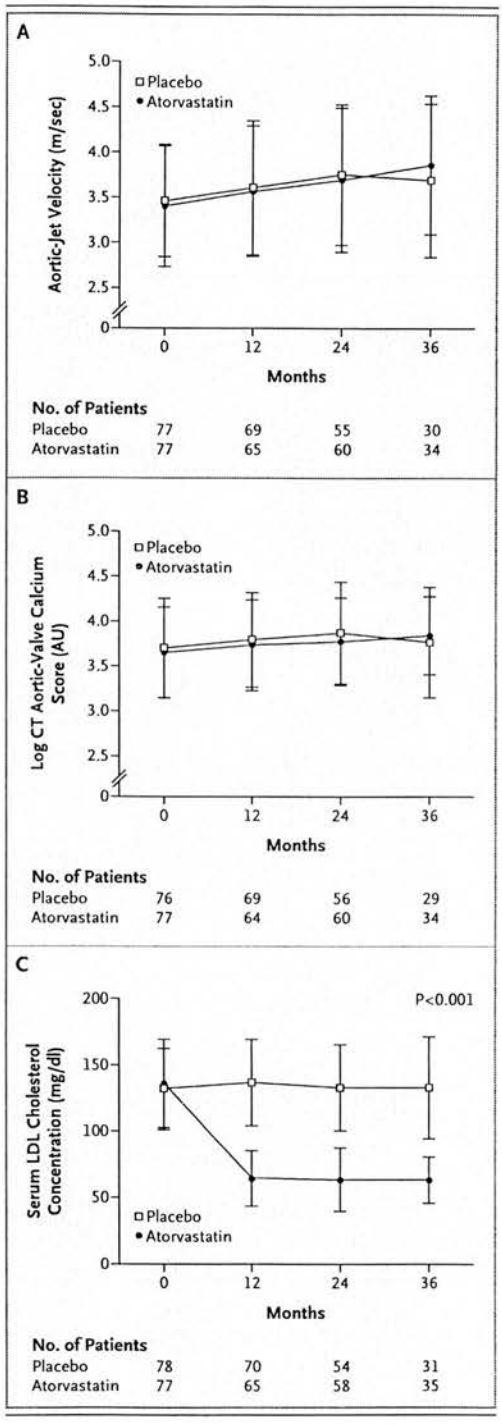
The mean serum low-density lipoprotein (LDL) cholesterol concentration remained at 130±30 mg per deciliter (3.4±0.8 mmol per liter) in the placebo group and decreased by 53 percent to 63±23 mg per deciliter (1.7±0.6 mmol per liter) in the atorvastatin group (P<0.001) (Fig. 1C). Serum total cholesterol was 209±35 mg per deciliter (5.5±0.9 mmol per liter) and 132±27 mg per deciliter (3.5±0.7 mmol per liter) in the placebo and atorvastatin groups, respectively (P<0.001), and is in keeping with 97 percent adherence to the study treatment in both groups, which was confirmed by a pill count.

EFFECT OF ATORVASTATIN ON DISEASE PROGRESSION

Intensive lipid-lowering therapy with 80 mg of atorvastatin daily had no effect on the rate of change in

Figure 1. **Progression in Aortic-Valve Stenosis and Serum LDL Cholesterol Concentrations in Patients Treated with Intensive Atorvastatin Therapy or Matched Placebo.**

Patients received 80 mg of atorvastatin daily or matched placebo. LDL denotes low-density lipoprotein, CT computed tomography, and AU arbitrary units. I bars indicate SDs.



aortic-jet velocity or valvular calcification (Table 2). Progression in valvular calcification was 22.3±21.0 percent per year in the atorvastatin group, and 21.7±19.8 percent per year in the placebo group (P=0.93; ratio of post-treatment aortic-valve calcium score, 0.998; 95 percent confidence interval, 0.947 to 1.050). We also performed a longitudinal analysis of the rate of change over time for the two treatment groups with the use of a mixed-effects linear model.[36] This showed no difference in the rate of disease progression, with point estimates and 95 percent confidence intervals for the treatment difference that were similar to those shown in Table 2 (mean difference in the rate of change of aortic-jet velocity [the change in the atorvastatin group minus that in the placebo group], 0.008 m per second per year [−0.058 to 0.075]; mean difference in rate of change of aortic-valve calcium score, 71 AU per year [−524 to 666]). Serum LDL cholesterol concentrations did not correlate with disease progression demonstrated on echocardiography (r=0.021, P=0.81) or CT (r=−0.109, P=0.21). The proportion of patients reaching secondary clinical end points seemed to be less in the atorvastatin group, but none of the comparisons achieved statistical significance (Table 3).

SUBGROUP ANALYSES

Prespecified subgroup analysis of the primary endpoint data was conducted in patients with mild-to-moderate aortic stenosis (aortic-jet velocity, <4.0 m per second) and severe aortic stenosis (aortic-jet velocity, ≥4.0 m per second) at baseline. As anticipated from earlier studies, patients with severe stenosis at baseline progressed more rapidly (P=0.04), but the study findings were consistent regardless of the severity of stenosis at baseline (Table 4).

Likewise, the length of follow-up did not influence outcome. In those followed for more than 24

Table 2. **Progression from Baseline of Aortic-Valve Stenosis on Echocardiography and Computed Tomography.***

Variable	All Patients	Atorvastatin	Placebo	Adjusted Difference: Atorvastatin–Placebo (95% CI)	P Value
Echocardiography					
No. of patients	134	65	69		
Change in aortic-jet velocity (m/sec/yr)	0.201±0.208	0.199±0.210	0.203±0.208	0.002 (−0.066 to 0.070)	0.95
Increase in peak gradient (mm Hg/yr)	6.52±7.24	6.48±7.43	6.56±7.10	0.21 (−2.02 to 2.45)	0.85
Change in aortic-valve area (cm^2/yr)	−0.081±0.107	−0.079±0.107	−0.083±0.107	0.007 (−0.026 to 0.040)	0.68
Computed tomography					
No. of patients	133	64	69		
Absolute change in aortic-valve calcium score (AU/yr)	1608±1865	1564±1956	1648±1790	85 (−554 to 723)	0.80
Change in log aortic-valve calcium score (per yr)	0.20±0.16	0.20±0.16	0.20±0.15	0.00 (−0.05 to 0.05)	0.93

* Plus–minus values are means ±SD. CI denotes confidence interval, and AU arbitrary units.

Table 3. **Number of Patients Reaching Secondary End Points.**

Secondary End Point	Atorvastatin (N=77)	Placebo (N=78)	P Value (Fisher's Exact Test)
Composite*	13	21	0.19
Death from cardiovascular causes	3	3	1.00
Aortic-valve replacement	11	19	0.17
Hospitalization for severe aortic stenosis	3	5	0.73
Death from any cause	3	5	0.73
Hospitalization for any cause	10	12	0.84

* The composite end point was death from cardiovascular causes, aortic-valve replacement, or hospitalization for severe aortic stenosis.

months (median, 33), the increase in aortic-jet velocity was 0.21±0.20 m per second per year in the atorvastatin group and 0.17±0.14 m per second per year in the placebo group (Table 4). In those followed for 24 months or less (median, 23), the increase in aortic-jet velocity was 0.19±0.22 m per second per year in the atorvastatin group and 0.23±0.25 m per second per year in the placebo group.

ADVERSE EVENTS

There were similar rates of adverse events in the two treatment groups. Four patients (5 percent) in the placebo group and seven patients (9 percent) in the atorvastatin group discontinued the study drug (P=0.52 by Fisher's exact test), predominantly as a result of gastrointestinal symptoms. Three patients in the atorvastatin group had an increase in the creatine kinase level to more than five times the upper limit of the normal range, without symptoms of myositis; one of these patients was withdrawn at the request of the data-monitoring committee. There were no cases of rhabdomyolysis and no serious adverse events.

DISCUSSION

In this randomized, double-blind, placebo-controlled, parallel-group trial of lipid-lowering therapy in patients with calcific aortic stenosis, a single coordinating center used a consistent and reproducible approach to assess the severity of aortic stenosis.[33] We have clearly shown that high-dose atorvastatin reduces serum LDL cholesterol concentrations by more than a factor of two, as anticipated,[37] but it does not halt the progression or induce regression of the valvular disease process. This was shown with the use of two distinct measures of disease severity — aortic-jet velocity assessed with Doppler echocardiography and valvular calcification assessed with helical CT. Moreover, there was no relationship between serum LDL cholesterol concentrations and the progression of aortic stenosis, nor did high-dose atorvastatin have a demonstrable effect on clinical end points. Thus, regardless of the method of assessing disease progression, we have consistently shown that aortic stenosis progresses despite intensive reductions in serum cholesterol concentrations.

The minimization technique helped ensure that there were no baseline inequalities between the

Table 4. **Subgroup Analyses of Disease Progression According to Aortic-Jet Velocity.***

Characteristic	Atorvastatin				Placebo			
	No.	Baseline Value	No.	Rate of Change	No.	Baseline Value	No.	Rate of Change
		m/sec		*m/sec/yr*		*m/sec*		*m/sec/yr*
Baseline severity of stenosis†								
Mild to moderate	58	3.12±0.43	49	0.17±0.21	61	3.18±0.44	55	0.19±0.20
Severe	19	4.24±0.21	16	0.27±0.21	17	4.45±0.26	14	0.27±0.23
Duration of follow-up								
≤24 Mo‡	30	3.49±0.69	30	0.19±0.22	37	3.64±0.67	37	0.23±0.25
>24 Mo§	35	3.31±0.55	35	0.21±0.20	32	3.28±0.61	32	0.17±0.14

* Plus–minus values are means ±SD. P=0.57 for the interaction of treatment and the baseline severity of stenosis, and P=0.41 for the interaction of treatment and the duration of follow-up.
† Patients with mild-to-moderate aortic stenosis had an aortic-jet velocity of less than 4.0 m per second, and those with severe stenosis an aortic-jet velocity of at least 4.0 m per second.
‡ The median follow-up was 23 months.
§ The median follow-up was 33 months.

treatment groups. Several factors may have influenced our ability to detect an effect of statin therapy on the progression of aortic stenosis in this trial. First, as a consequence of our inclusion criteria, we recruited some patients with severe disease and an aortic-jet velocity of at least 4 m per second, and it could be argued that lipid-lowering therapy is unlikely to influence disease progression at such an advanced stage. We therefore conducted a prespecified subgroup analysis excluding patients with a baseline aortic-jet velocity of 4 m per second or more. Our findings were consistent regardless of the severity of stenosis at baseline — atorvastatin had no effect on disease progression, even in the majority of patients with mild-to-moderate stenosis. We excluded patients with an aortic-jet velocity of less than 2.5 m per second, and we acknowledge that intervening at this earlier stage of the disease process may have been more beneficial. However, such patients do not commonly present to routine clinical practice, and their identification would potentially require population screening.

Second, two years of treatment may not have been sufficient to influence the natural history of the disease. We assessed this possibility by determining if patients with a longer follow-up showed a treatment benefit. In patients who underwent nearly three years of treatment with intensive statin therapy, no trend toward a beneficial effect of atorvastatin was apparent. Therefore, we do not believe that the lack of an effect was due to an inadequate treatment period.

Finally, our study was designed to detect a substantial delay in disease progression and was not powered to assess meaningful effects on clinical end points, such as valve replacement and cardiovascular death. Although we can exclude a treatment benefit of the magnitude previously reported in retrospective observational studies (a reduction in the aortic-jet velocity of 0.30 m per second per year[29] and valvular calcification of 30 percent per year[24,26]), the 95 percent confidence intervals indicate that we may have missed a modest treatment benefit (a delay in disease progression of <0.07 m per second per year for aortic-jet velocity and <5 percent per year for valvular calcification). Although such modest reductions are unlikely to be meaningful in the majority of older patients, a small decrease in disease progression may be clinically important in younger patients with mild disease that may progress over many years.

Given the strength of the data linking aortic stenosis with atherosclerosis and hypercholesterolemia, why have we failed to halt the progression of calcific aortic stenosis? One potential explanation is that, although these features may drive the initiation of aortic stenosis, disease progression may depend on other factors. The aortic valve is subject to continuous dynamic mechanical stress, and the plasticity and structure of the leaflets can have an overriding influence, as is the case with a bicuspid valve. Moreover, in contrast to atherosclerosis, aortic stenosis is associated with a virtual absence of smooth-muscle-cell proliferation and lipid-laden

macrophages[2] and is dominated by earlier and more extensive mineralization. Decreasing the lipid pool and strengthening the fibrous cap may be less relevant to the progression of aortic stenosis than they are for the reduction in atherosclerotic-plaque rupture with statin therapy in patients with coronary heart disease.

Because of the association between aortic stenosis and coronary artery disease, statin therapy in patients with aortic stenosis may confer secondary preventive benefits that are independent of its effects on the valvular disease process. The current study was not powered to assess the benefits of lipid-lowering therapy on cardiovascular end points such as nonfatal and fatal myocardial infarction. It remains a possibility that aortic stenosis and sclerosis[38] may be important markers of occult vascular disease and may identify patients who would gain from the preventive benefits of statin therapy.

We conclude that intensive lipid-lowering therapy with 80 mg of atorvastatin daily does not halt the progression of calcific aortic stenosis or induce its regression. Nevertheless, this trial does not rule out a small but potentially relevant reduction in the rate of disease progression or a significant reduction in major clinical end points. Our study reinforces the need for a long-term, large-scale, randomized, controlled trial of intensive lipid-lowering therapy in patients with calcific aortic stenosis, particularly in those with early, mild disease. In the meantime, we do not recommend statin therapy for patients with calcific aortic stenosis in the absence of coexisting vascular disease.

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APPENDIX

The following participated in the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE): **Research team:** L. Anderson, C. Bell, M. Bland, J. Burton, S. Cameron, N. Cruden, J. Cunningham, H. Cuthbertson, L. Flint, M. Henderson, D. Lyle, M. O'Donnell, F. Paterson, K. Paterson, S. Robinson, H. Spence, J. Tickner, A. White. **Collaborating centers (all in the United Kingdom):** *Borders General Hospital, Melrose* — P. Broadhurst, C. Norris, P. Leslie, J. Gaddie; *Eastern General Hospital, Edinburgh* — A. Elder; *Royal Infirmary, Edinburgh* — K. Fox, N. Grubb, A. Flapan, H. Miller, N. Uren; *Falkirk and District Royal Infirmary, Falkirk* — A. Hargreaves, P. McSorely; *Queen Margaret Hospital, Dunfermline* — D. MacLeod; *Roodland's Hospital, Haddington* — A. Flapan; *St. Johns' Hospital, Livingston* — J. Irving, A. Jacob; *Royal Infirmary, Stirling* — A. Bridges, S. Glen; *Wellcome Trust Clinical Research Facility, Edinburgh; Western General Hospital, Edinburgh* — M. Denvir, T. Shaw, I. Starkey. **Pharmacy:** *Royal Infirmary, Edinburgh* — B. Booth; *Freeman Hospital, Newcastle-upon-Tyne, United Kingdom* — A. Heed. **Medical Statistics:** *University of Edinburgh, Edinburgh* — T. Forster.

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CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see N Engl J Med 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.

CARDIOVASCULAR MEDICINE

Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial

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Objectives: To evaluate the effect of intensive lipid-lowering treatment on coronary artery calcification in a substudy of a trial recruiting patients with calcific aortic stenosis.

Methods: In a double blind randomised controlled trial, 102 patients with calcific aortic stenosis and coronary artery calcification were randomly assigned by the minimisation technique to atorvastatin 80 mg daily or matched placebo. Coronary artery calcification was assessed annually by helical computed tomography.

Results: 48 patients were randomly assigned to atorvastatin and 54 to placebo with a median follow up of 24 months (interquartile range 24–30). Baseline characteristics and coronary artery calcium scores were similar in both groups. Atorvastatin reduced serum low density lipoprotein cholesterol (−53%, $p < 0.001$) and C reactive protein (−49%, $p < 0.001$) concentrations whereas there was no change with placebo (−7% and 17%, $p > 0.95$ for both). The rate of change in coronary artery calcification was 26%/year (0.234 (SE 0.037) log arbitrary units (AU)/year; n = 39) in the atorvastatin group and 18%/year (0.167 (SE 0.034) log AU/year; n = 49) in the placebo group, with a geometric mean difference of 7%/year (95% confidence interval −3% to 18%, $p = 0.18$). Serum low density lipoprotein concentrations were not correlated with the rate of progression of coronary calcification ($r = 0.05$, $p = 0.62$).

Conclusion: In contrast to previous observational studies, this randomised controlled trial has shown that, despite reducing systemic inflammation and halving serum low density lipoprotein cholesterol concentrations, statin treatment does not have a major effect on the rate of progression of coronary artery calcification.

Coronary artery calcification is an independent risk factor for coronary heart disease, with even low coronary calcium scores doubling the risk of coronary events.[1] The relative risk associated with coronary calcification is greater than that associated with established factors such as smoking, hypertension and diabetes mellitus. Progression of coronary artery calcification is associated with a higher incidence of coronary events even among people who are asymptomatic at the time of initial scanning.[2] Thus, not only is the presence of coronary artery calcification indicative of atheromatous plaque disease but its progression may correspond with cardiovascular event rates.

Statin treatment has a proven role in the primary[3 4] and secondary prevention[5–8] of cardiovascular disease, with incremental benefits seen with more intensive reductions in serum cholesterol concentrations.[8] Previous studies[9 10] have reported that statins can halt the progression and may even induce regression of coronary artery calcification. Indeed, the rate of progression of coronary artery calcification correlates with the average serum low density lipoprotein (LDL) cholesterol concentration.[9] This has led to the use of computed tomography to monitor disease progression and response to treatment, particularly with statins. Two recent trials, however, did not show a benefit of statin on the progression of coronary artery calcification in asymptomatic people.[11 12]

The SALTIRE (Scottish Aortic Stenosis Lipid lowering Therapy, Impact on Regression) trial was a prospective double blind, randomised controlled study of intensive lipid-lowering treatment of patients with calcific aortic stenosis.[13] As part of this trial, aortic valve and coronary artery calcium scores are measured by helical computed tomography. The objective of this substudy was to assess the effect of atorvastatin 80 mg daily on the rate of progression of coronary artery calcification in patients with calcific aortic stenosis.

METHODS

Patient population

Patients aged > 18 years with calcific aortic stenosis (grade 1–3 calcification on echocardiography[14]) and a peak post valve velocity of ⩾ 2.5 m/s were recruited from eight hospital centres across the southeast of Scotland. Exclusion criteria were women of childbearing potential without contraception, active or chronic liver disease, history of alcohol or drug misuse, severe mitral stenosis (valve area < 1 cm^2), severe mitral or aortic regurgitation,[15] major left ventricular dysfunction (ejection fraction < 35%), planned aortic valve replacement, intolerance to statins, patients who were taking or would in the opinion of the treating physician benefit from statins, baseline serum total cholesterol of < 4.0 mmol/l, and permanent pacemaker or cardiodefibrillator. For the substudy, we also excluded patients who had no coronary artery calcification on computed tomography. The study was conducted with the approval of all the regional research ethics committees and in accordance with the Declaration of

Abbreviations: AU, arbitrary units; BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning; CRP, C reactive protein; LDL, low density lipoprotein; SALTIRE, Scottish Aortic Stenosis Lipid Lowering Therapy, Impact on Regression

Helsinki. Written informed consent was obtained from each participant.

Study protocol

Between March 2001 and April 2002, the blinded study coordinator randomly assigned eligible patients by the minimisation technique[16] with a dedicated locked computer program (Edinburgh University), which incorporated eight baseline variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, peak aortic jet velocity and aortic calcium score. Patients were assigned either to atorvastatin 80 mg daily or matched placebo (Pfizer, Tadworth, UK) as a single daily dose in numbered containers.

Patients were assessed at baseline, two months, six months and every six months thereafter for a minimum of two years. Clinical evaluation included assessment of functional status, adverse events and biochemical blood analysis. Serum high sensitivity C reactive protein (CRP) concentrations were determined by a highly sensitive immunonephelometric method (Dade Behring, Milton Keynes, UK) as previously described.[17] All patients underwent computed tomography within the month before randomisation to study treatment and at each annual visit. Randomly assigned patients who were later treated with an open label statin by their attending physician were immediately scanned and withdrawn from further observation.

Computed tomography

A single blinded operator performed computed tomography with a double helix scanner (Twin II Flash; Philips Medical Systems (UK), Stevenage, UK) calibrated against a standard phantom. Images were acquired in 2.7 mm slices (with a 0.75 s full 360° scan mode) through the region of the coronary arteries with a pitch of 0.7 and an increment of 1.3 mm during held inspiration. Exposure factors were 120 kV at 270 mA and the scan angle was 360°. Images were analysed off line with an automated, computerised software program (Picker cardiac scoring). This uses an Agatston scoring method,[18] producing sensitivity and specificity comparable with electron beam computed tomography.[17] Scans were scored by both the Agatston (130 HU threshold) and the modified Agatston (90 HU threshold) methods.[19] The Agatston method has been shown to reduce interobserver and interscan variation compared with the threshold of 90 HU.[20] To assess the reproducibility of the method, repeated baseline computed tomography scans were recorded within four weeks of each other in an unselected random sample of 16 patients.

Data analysis and statistics

Coronary artery calcium scores are expressed in arbitrary units (AU) based on the 130 HU threshold. The calcium scores and high sensitivity CRP concentrations were not normally distributed and data are presented as median

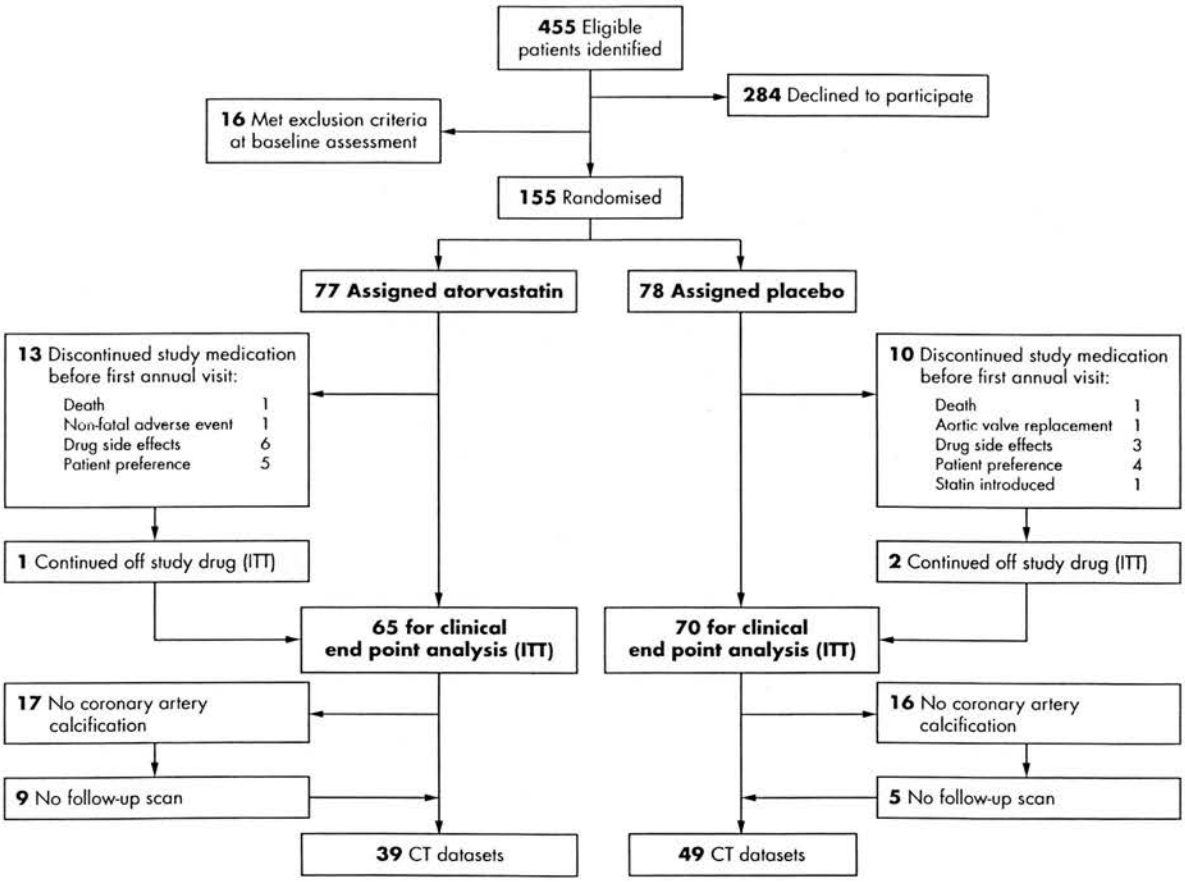

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients recruited into the trial and substudy. CT, computed tomography; ITT, intention to treat.

Table 1 Baseline characteristics of participants with calcific aortic stenosis in the treatment groups

Characteristic	Atorvastatin (n=39)	Placebo (n=49)
Age (years)	70 (8)	70 (9)
Men	74%	78%
Body mass index (kg/m^2)	29 (5)	28 (5)
Cardiovascular risk factors		
Hypertension	22	28
Hyperlipidaemia	3	2
Diabetes mellitus	0	2
Current smoker	5	10
Cardiovascular disease		
Coronary heart disease	7	13
Cerebrovascular disease	5	7
Peripheral vascular disease	3	7
Drug history		
Aspirin	17	26
ACE inhibitor	7	8
β blocker	11	15
Warfarin	4	8
Blood pressure (mm Hg)		
Systolic	143 (18)	140 (19)
Diastolic	82 (11)	78 (11)
Lipid profile		
Total cholesterol (mmol/l)	5.7 (0.9)	5.5 (0.9)
LDL cholesterol (mmol/l)	3.6 (0.8)	3.4 (0.7)
HDL cholesterol (mmol/l)	1.5 (0.4)	1.5 (0.4)
Total cholesterol:HDL	4.2 (1.2)	4.0 (1.0)
Triglycerides (mmol/l)	1.5 (0.8)	1.4 (0.7)
Coronary calcification score (AU)		
Left anterior descending artery	112 (40–285)	207 (76–461)
Circumflex artery	0 (0–9)	0 (0–4)
Right coronary artery	0 (0–29)	0 (0–0)
Total coronary score	195 (57–448)	235 (83–526)
Log total coronary score (log AU)	2.16 (0.68)	2.30 (0.65)

Continuous variables stated as mean (SD) or median (interquartile range).
ACE, angiotensin-converting enzyme; AU, arbitrary unit; HDL, high density lipoprotein; LDL, low density lipoprotein.

(interquartile range) or mean (SD) after logarithmic transformation (log AU). The primary end point, the rate of change of coronary calcium scores, was analysed with random coefficient models[13 21] after logarithmic transformation of the scores. In summarising the data, we calculated the change in coronary artery calcium scores by dividing the change between the baseline and final scores by the duration of follow up. Rate of change in coronary calcium score is expressed as percentage change per year or as absolute change in the logarithm of the coronary artery calcium score. Reproducibility was assessed by the method of Bland and Altman.[21] As well as tests of significance, 95% confidence intervals are reported as appropriate. Significance was taken as a two-sided $p < 0.05$.

RESULTS

Of 155 patients recruited into the SALTIRE trial, 102 had coronary calcification at baseline (fig 1), of whom 88 had at least two scans. Coronary calcification predominated in the left anterior descending artery (100% of patients) although it was also present in the circumflex (33%) and right (27%) coronary arteries. Baseline characteristics and coronary artery calcium scores were well matched in both treatment groups (table 1) in the 88 evaluable participants.

Reproducibility

The reproducibility of the left anterior descending coronary score and of the total coronary score was examined with the approach of Bland and Altman.[21] Without transformation, the difference between replicate observations tended to increase with the magnitude of the measurement. After logarithmic transformation, higher values showed stable differences, but differences were higher at the lowest scores. Overall, the differences on the log scale correspond to a coefficient of variation of 28% for both variables, but when the analysis was restricted to the 10 pairs with a geometric mean score above 100, the coefficient of variation was 10% for both variables.

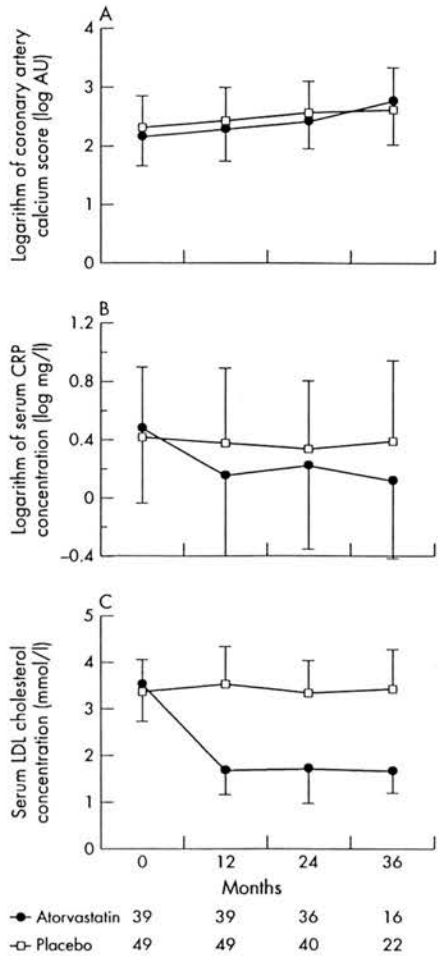

Figure 2 Progression of (A) coronary artery calcification, (B) serum C reactive protein (CRP) concentrations ($p < 0.001$, atorvastatin *v* placebo) and (C) serum low density lipoprotein (LDL) cholesterol concentrations ($p < 0.001$, atorvastatin *v* placebo) in patients treated with atorvastatin 80 mg daily or matched placebo. AU, arbitrary units.

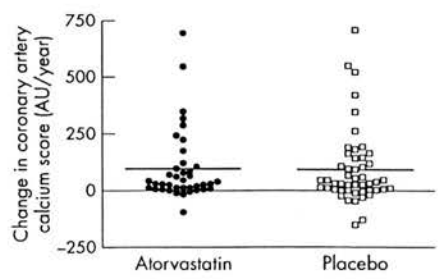

Figure 3 Absolute rate of change in coronary calcium score expressed in arbitrary units (AU) per year for patients treated with atorvastatin 80 mg or matched placebo.

Effect of atorvastatin treatment

Patients were followed up for a median of 24 months (interquartile range 24–30). Atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations (53 (SD 19)%, $p < 0.001$), whereas placebo had no effect (fig 2). This reduction in serum LDL cholesterol concentrations was associated with a major decrease in serum CRP concentrations from 1.95 (interquartile range 1.15–4.86) to 1.00 mg/l (0.49–2.31) (Wilcoxon signed rank test $p < 0.001$) (fig 2). Atorvastatin was well tolerated: two patients in the placebo group and five patients in the atorvastatin group discontinued the treatment, predominantly as a result of gastrointestinal upset. One patient taking atorvastatin had an increase in creatine kinase of > 5 times the upper limit of normal without symptoms of myositis and was withdrawn at the request of the Data Monitoring Committee. There were no cases of rhabdomyolysis.

Coronary artery calcium score

Atorvastatin did not affect the rate of progression of the coronary artery calcium score (fig 2). Similar results were obtained when the 90 HU threshold was used (42 (SD 73)%/year in the atorvastatin group and 29 (SD 37)%/year in the placebo group, $p = 0.24$). Serum LDL cholesterol concentrations did not correlate with the rate of progression of coronary artery calcification ($r = 0.05$, $p = 0.62$).

The rates of change of coronary artery calcium scores were primarily analysed on the logarithms of the scores by random coefficients models.[22] This showed no difference between the average rates of change in the two treatment arms ($p = 0.18$). The mean coronary calcium score increased by 0.234 (SE 0.037) log AU/year in the atorvastatin group and 0.167 (SE 0.034) log AU/year in the placebo group. These figures correspond to a 26%/year increase in the atorvastatin group and 18%/year in the placebo group. The geometric mean (adjusted for baseline) is 7% higher at one year with atorvastatin than with placebo, with 95% confidence limits ranging from 3% lower to 18% higher. Figure 3 summarises the observed annual changes in coronary calcium scores, calculated from the first to the last visit.

As anticipated in such a modest clinical trial, all cause mortality, cardiovascular mortality or cardiovascular hospitalisation did not differ significantly between the two groups.

DISCUSSION

We have confirmed that, despite major reductions in serum LDL cholesterol and CRP concentrations, atorvastatin 80 mg daily did not halt the progression, or induce regression, of coronary artery calcification in patients with calcific aortic stenosis. Consistent with recent trials of asymptomatic people,[11 12] our findings contrast notably with previous observational studies and suggest that the potential beneficial effects on coronary artery calcification have been overestimated.

Previous observational and non-randomised prospective studies[9 10] have suggested that reductions in serum LDL cholesterol concentrations decrease the progression of coronary calcification. Not all observational studies, however, have had consistent findings. In the largest observational study of 182 patients, Hecht and colleagues[23] recently found no difference in the progression of coronary calcium scores in patients who were maintained on lipid-lowering treatment and achieved significant reductions in serum LDL cholesterol concentrations. Observational data may be misleading and prospective randomised controlled trials are necessary to confirm or to refute these interesting preliminary observations. The recent BELLES (Beyond Endorsed Lipid Lowering with EBT Scanning) trial[12] found no differential effect between pravastatin (40 mg daily) and atorvastatin (80 mg daily) on the progression of coronary artery calcification in 615 hyperlipidaemic postmenopausal women. Study follow up was brief (one year), however, and there was no placebo control group. The St Francis Heart Study[11] randomly assigned 1005 asymptomatic middle-aged men and women with high coronary artery calcium scores to combination atorvastatin 20 mg, vitamin C 1 g, and vitamin E (α tocopherol) 1000 U daily or to matching placebos. After 4.3 years of follow up, the rate of progression of coronary artery calcification did not differ.

We have conducted a double blind randomised controlled trial with helical computed tomography in patients with aortic stenosis. Minimisation technique ensured good matching of the baseline characteristics of the patient population and reproducibility studies confirmed the validity of our repeated assessments. Although documenting very similar rates of progression of coronary calcification to previous studies,[9 10 23] we have not observed a reduction in coronary calcification with intensive lipid-lowering treatment despite more than halving serum LDL cholesterol concentrations.

Statins have been extremely successful in the primary and secondary prevention of cardiovascular disease. Why then have we and others not observed a beneficial effect of statin on coronary artery calcification? Unstable atherosclerotic plaques have a large lipid-rich core, a preponderance of macrophages and foam cells, and a thin fibrous cap containing few smooth muscle cells.[24] It has been suggested that calcified lesions may be relatively more stable,[25] indicating a possible protective role of calcification in coronary plaques. Statins produce many of their beneficial effects through plaque stabilisation. In both primate[26] and swine[27] models, antiatherosclerotic interventions are associated with an increase in vascular fibrous tissue and calcification. This calcium deposition continues during the initial phase of plaque regression due to the death of foam cells and an increase in necrotic tissue. Thus, vascular calcification may have a role in the initial stabilisation of atherosclerotic plaques. This is consistent with our findings and would account for the lack of effect on the progression of coronary artery calcification despite a reduction in serum CRP concentrations.

After the initial stabilisation of the atherosclerotic plaque, subsequent progression of coronary calcification would be anticipated to be inhibited. The present study was brief, and follow up was only continued for a median of two years. It would be important to extend our observations to five or more years to assess properly the impact of statin on the long-term progression of coronary artery calcification. It should be acknowledged, however, that the clinical benefits of statin are apparent within the first few years,[6–8] and in some cases the first few months,[28] of treatment. Moreover, the St Francis Heart Study showed no beneficial effects despite 4.3 years of follow up.[9]

On the basis of previous non-randomised studies,[10] the practice of performing serial computed tomography to monitor disease progression and the response to treatment has become widespread, especially in North America. Our data, and those of the St Francis Heart Study[11] and the BELLES study,[12] indicate that repeated scanning to assess response to statin is not justified. Indeed, the radiation dose incurred for such serial scans poses potential health risks, particularly when multidetector computed tomography scanners are used.

Study limitations

Several factors should be taken into account when considering the results of our study. This was a substudy of the SALTIRE trial[13] that recruited only patients with calcific aortic stenosis. Our findings are consistent, however, with two

recent randomised controlled trials in asymptomatic younger people without valvular heart disease.[11 12] Our study therefore suggests that failure of statins to restrict the progression of coronary artery calcification can be extended to include patients with valvular heart disease as well as older populations. Moreover, our findings suggest that the lack of benefit seen in the St Francis Heart Study is not attributable to the modifying effects of antioxidant vitamins.

When compared with electron beam computed tomography, the accuracy of helical computed tomography in detecting coronary artery calcification has been questioned.[18 29] Technological advances have also meant that double helical scanners have now been overtaken by 64-slice scanners. At trial inception, the double helix scanner was the latest technology, and it would have been inappropriate to replace the scanner during the conduct of the trial. Moreover, our approach has been previously validated[21] and we have shown good reproducibility of coronary artery calcification scores in patients with scores of > 100 AU. We do not believe the absence of a major beneficial effect on coronary artery calcification is attributable to our methods. We acknowledge that our population size is modest; however, the 95% confidence intervals can exclude a relative reduction in progression of coronary artery calcification of > 3%/year. We therefore suggest that if lipid-lowering treatment does reduce the progression of coronary artery calcification then the effect is rather small.

The method of quantification of coronary artery calcification is controversial. The Agatston method is traditionally used but this may overestimate the coronary calcium score in newer generation scanners with reduced slice thickness due to partial voluming. More recent methods include the volume[30] and the coronary calcium mass[31] scores, although neither is superior to the Agatston score in terms of reproducibility from consecutive scans in an individual patient.[32]

Conclusion

We conclude that intensive lipid-lowering treatment does not halt the progression, or induce regression, of coronary artery calcification. Although coronary artery calcium scores correlate well with the presence of atherosclerosis and predict future coronary risk, our findings confirm that monitoring progression of coronary artery calcification to assess the response to lipid-lowering treatment has no role.

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Competing interests: DEN and NAB hold unrestricted educational grant awards from Pfizer (UK) Ltd. DEN, DBN and NAB have undertaken paid consultancy and served on advisory boards for Pfizer (UK) Ltd.

Author contributions: ESH, SJC, JB and JR acquired the data. ESH and RP analysed the data. DEN, DBN and NAB conceived and designed the study. All authors contributed to the writing, revision and approval of the paper.

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IMAGES IN CARDIOLOGY

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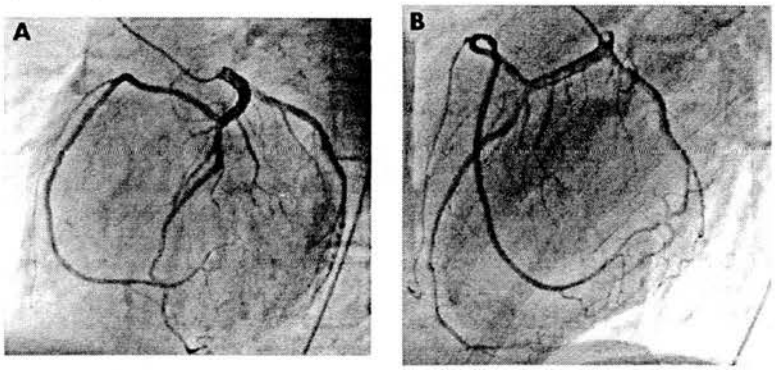
Anomalous origin of right coronary artery from the mid left anterior descending coronary artery

A 59-year-old women underwent diagnostic coronary angiography with a history of atypical chest pain and an inconclusive treadmill exercise tolerance test. Cine-angiogram revealed an unusual origin of the right coronary artery (RCA) arising from the mid left anterior descending coronary (LAD) artery and coursing to the right, anterior to the right ventricular outflow tract. Such an anomaly is unusual and has not been listed in the classification of such anomalies.

Coronary anomalies are seen in about 1% of cineangiograms. While some anomalies have been associated with adverse clinical outcomes, most are benign. The RCA has been documented to have an anomalous origin from the left anterior coronary sinus and pulmonary trunk, but the origin of the RCA from the LAD has not been reported before.



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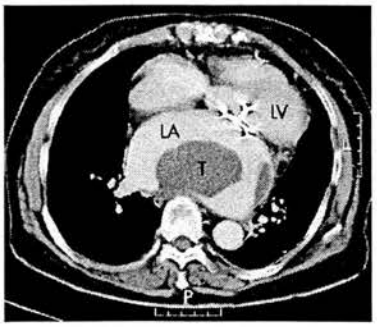
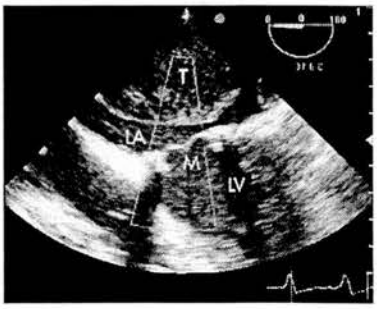
Huge left atrial thrombus in a patient with mitral bioprosthesis

A 77-year-old woman had suffered from atrial fibrillation and rheumatic mitral stenosis for more than 20 years. She underwent mitral valve replacement with bioprosthesis six months before her admission. Inadequate anticoagulation treatment was noted during the follow-up period. She presented with unsteady gait and dizziness to our emergency room. Brain magnetic resonance images confirmed cerebellar infarction. Echocardiography was arranged to search for the possible embolus source, and revealed a huge left atrial thrombus. Because of the thrombus burden and recent stroke, redo cardiac surgery was proposed three weeks after the cerebrovascular event. The preoperative computed tomography (CT) for redo surgery found a large left atrial mass (left panel). During the less invasive cardiac surgery via right small thoracotomy, transoesophageal echocardiography revealed the significant thrombus burden again (right panel). The bioprosthesis was found to be functioning well and thrombus-free. Additional left atrial appendage closure and endocardial ablation were performed to reduce the risk of future thromboembolism.



Computed tomography demonstrating a huge mass in an enlarged left atrium. LA, left atrium; LV, left ventricle; T, thrombus.



Transoesophageal echocardiography revealing a heavy thrombus burden in the posterior wall of left atrium with the bioprosthesis in the mitral position (M).

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HEART REVIEW

Emerging medical treatments for aortic stenosis: statins, angiotensin converting enzyme inhibitors, or both?

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Aortic stenosis is the most common adult heart valve condition seen in the Western world and its incidence continues to rise. No established disease modifying treatments retard progression of the stenotic process. Recent insights into the pathogenesis of calcific aortic stenosis suggest that the disease mimics atherosclerosis. The natural history and progression of calcific aortic stenosis are described with particular emphasis on new and emerging medical treatments that may modify the disease process. In particular, statins and angiotensin converting enzyme inhibitors appear to hold promise but definitive evidence from large clinical trials is awaited.

Aortic stenosis is the most common adult heart valve condition seen in the Western world. It is predominantly due to "degenerative" calcific disease, although it can be a consequence of congenital disease such as a bicuspid aortic valve and rheumatic heart disease or of a rare metabolic disease such as ochronosis. Watchful waiting and the judicious use of aortic valve replacement surgery remains the mainstay of its management and treatment. We describe here the aetiology and natural history of calcific aortic stenosis and discuss the prospect of developing medical treatments that can modify the disease process.

NATURAL HISTORY OF CALCIFIC AORTIC STENOSIS

Calcific aortic stenosis has been recognised for over a century. Recently it has been suggested that aortic sclerosis may be the earliest manifestation of this disease process: sclerosis arising from the development of valvar calcific lesions that progress slowly over many years before ultimately causing aortic stenosis.[1] The current prominence of calcific aortic valve disease probably results from increased human longevity associated with the declining prevalence of rheumatic fever.

Calcific aortic stenosis is a progressive condition, characterised by a long asymptomatic phase lasting several decades, followed by a shorter symptomatic phase usually associated with severe narrowing of the aortic valve orifice. The outlook for patients with asymptomatic disease is generally good but the prognosis changes dramatically with the onset of symptoms in association with severe outflow obstruction—a two year survival rate of about 50%.[2]

Despite the favourable outlook for patients with mild asymptomatic disease, the risk of cardiovascular events unrelated to the aortic valve disease is increased. Otto *et al*[2] reported that patients with aortic sclerosis have a 50% increased risk of myocardial infarction and cardiovascular death even in the absence of significant outflow tract obstruction. The Helsinki aging study also indicated that patients with moderate to severe aortic stenosis were at an increased risk of all cause and cardiovascular death irrespective of associated symptoms.[3]

PATHOLOGY OF CALCIFIC AORTIC STENOSIS

Historically, calcific aortic stenosis has been attributed to prolonged "wear and tear" and age associated valve degeneration. However, recent evidence suggests that it may be the result of an active inflammatory process involving biochemical, humoral, and genetic factors.

Normal aortic valve leaflets appear smooth, thin, and opalescent, with clearly defined tissue layers and very few cells. Increasing age gives rise to thickening of the tips of the valve leaflets, with an increase in the number of adipose cells and thinning of tissue layers.[4] Calcific aortic stenosis is characterised by leaflet thickening, with irregular nodular masses on the aortic aspect of the valve. Microscopic assessment of both mild and severely affected valves shows endothelial and basement membrane disruption, with underlying subendothelial thickening. The lesion itself contains disorganised collagen fibres, chronic inflammatory cells, lipids, extracellular bone matrix proteins, and bone mineral.[4]

The histological features described closely resemble those seen in atherosclerosis and are strongly suggestive of chronic inflammation (fig 1). The factors initiating the inflammatory process have not been identified but mechanical injury to the endothelium is thought to pave the way for subsequent inflammation. Indeed, the disease tends to affect the aortic surface of the leaflets and the non-coronary cusp that correspond to areas of low shear and high tensile stress. Congenitally bicuspid aortic valves are less efficient than tricuspid valves at distributing mechanical stress leading to the more rapid development of stenosis.

See end of article for authors' affiliations

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Abbreviations: ACE, angiotensin converting enzyme; ASTRONOMER, aortic stenosis progression observation: measuring effect of rosuvastatin; LDL, low density lipoprotein; SALTIRE, Scottish aortic stenosis and lipid lowering therapy, impact on regression; SEAS, simvastatin and ezetimibe in aortic stenosis

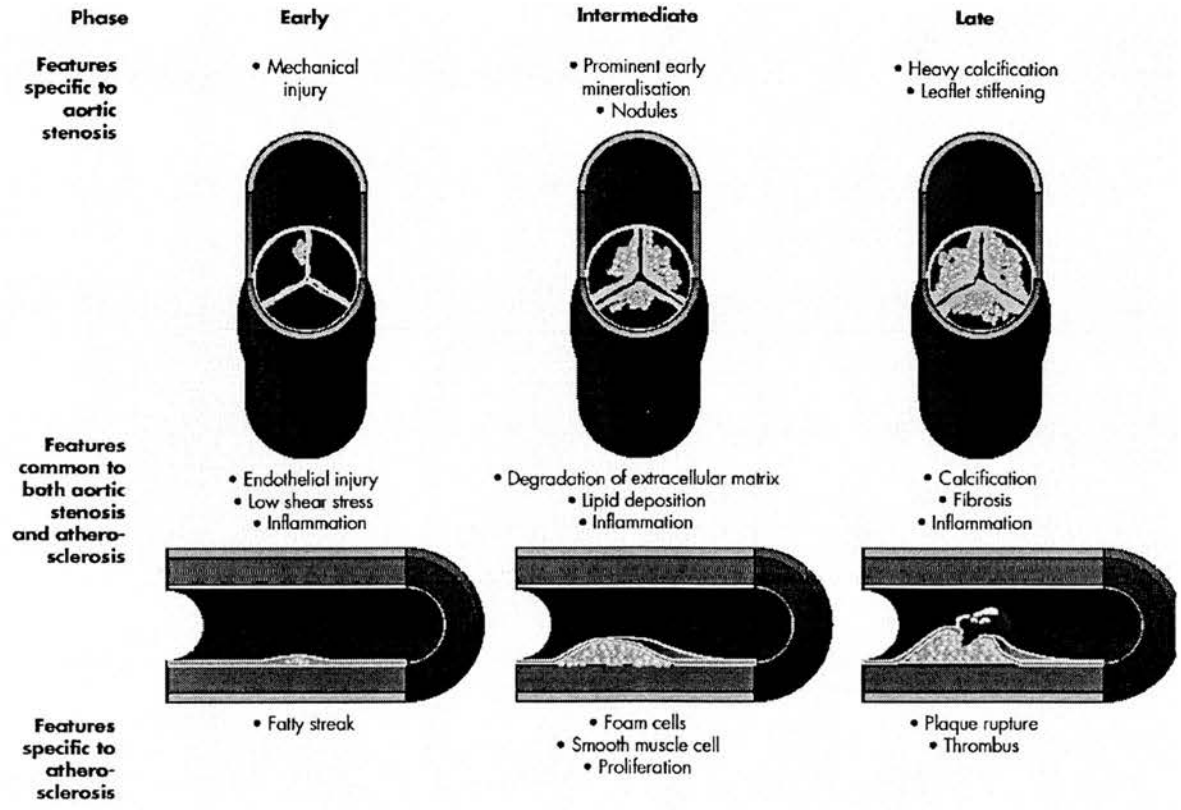

Figure 1 Common and specific pathogenetic features of aortic stenosis and atherosclerosis.

Lipids

Endothelial injury or disruption may allow lipids to penetrate the valvar interstitial tissue and accumulate in areas of inflammation.[5 6] The lipoproteins implicated in atherogenesis, including low density lipoprotein (LDL) and Lp(a) lipoprotein, are present in early aortic valve lesions and undergo oxidative modification.[5 6] These oxidised lipoproteins are highly cytotoxic and capable of stimulating inflammatory activity and mineralisation.[7]

Inflammation and calcification

Both macrophages and activated T lymphocytes are present in the early and advanced lesions of congenitally bicuspid and tricuspid aortic valves.[4] Migration of these effector inflammatory cells appears to be mediated through increased endothelial expression of cellular adhesion molecules such as E selectin, intercellular adhesion molecule 1, and vascular cell adhesion molecule 1. Once recruited into the subendothelium, the inflammatory cells release enzymes, such as matrix metalloproteinases, that degrade collagen, elastin, and proteoglycans within the aortic valve cusps.

Mineralisation is a characteristic of both atherosclerotic and aortic valve lesions and arises close to areas of inflammation. It is a prominent feature in calcific aortic stenosis and has been observed in early as well as advanced lesions.[4 8] Surgically excised valves have even shown areas of mature lamellar bone, haemopoietic marrow, and bone remodelling.[8] Some features suggest the presence of an active highly regulated process closely resembling developmental bone formation.[9]

The initiation of mineralisation (nucleation) may be stimulated by the presence of cellular degradation products following apoptosis or by the presence of oxidised lipids.[6 8] In vitro studies of cultured explants of stenotic valves have identified cells with osteoblastic characteristics capable of phenotypic differentiation and spontaneous calcification. Their origin is unknown but they may be derived from a pool of circulating immature pluripotent mesenchymal cells. These osteogenic cells or "calcifying valvar cells" express and produce a variety of regulatory bone matrix proteins including osteopontin and bone morphogenetic protein.[8]

CALCIFIC AORTIC STENOSIS AND ATHEROSCLEROSIS

Although the similarities with atherosclerosis were recognised as long ago as 1917, they were largely disregarded until recently. Histological studies have highlighted the common features but also confirmed differences in the cellular and mineral components of the two lesions.

Smooth muscle proliferation and lipid laden macrophages (or foam cells) are prominent features of vascular atheroma but are virtually absent from stenotic aortic valves (fig 1). Furthermore, mineralisation occurs earlier and is a more extensive feature of aortic valve lesions than in atherosclerosis.[4] These differences may, in part, explain why only 40% of patients with severe aortic stenosis have significant coronary artery disease and why the majority of patients with coronary artery disease do not have aortic stenosis.[10] As the underlying pathological processes of the two conditions appear to be similar, other unknown factors are likely to influence the development of valvar as opposed to vascular lesions.[11]

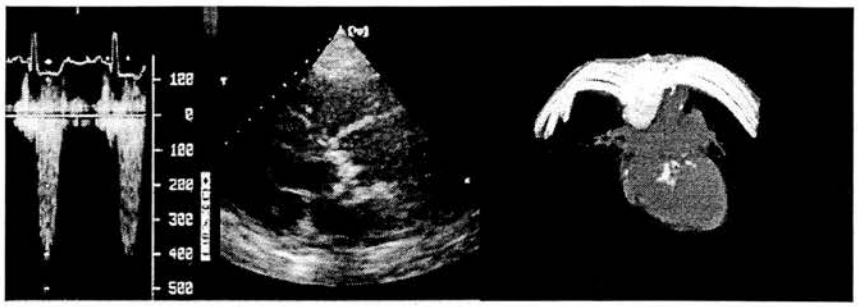

Figure 2 Clinical assessment by (A) Doppler echocardiography; (B) two dimensional echocardiography (parasternal short axis view); and (C) three dimensional computed tomography of the severity (lower panel) of aortic stenosis.

Aortic valve	Normal	Mild	Moderate	Severe
Peak velocity (m/s)	1–2	2–3	3–4	>4
Peak gradient (mm Hg)	0	16–36	36–64	>64
Mean gradient (mm Hg)	0	<15	15–50	>50
Valve area (cm^2)	>2.0	2.0–1.2	0.8–1.2	<0.8

PREDICTORS OF DISEASE PROGRESSION AND CLINICAL OUTCOME

Patients with calcific aortic stenosis should be monitored regularly in the clinic for the development of symptoms: chest pain, breathlessness, and syncope. Progression of the valvar stenosis is principally monitored with Doppler echocardiography, although complementary clinical information can also be obtained from the ECG (left ventricular hypertrophy, heart block), two dimensional echocardiography, and computed tomography. This permits grading of the severity of the aortic stenosis (fig 2).

The natural history of aortic stenosis is for the valve gradient to rise inexorably with time. Disease progression and clinical outcome have been linked to many of the risk factors for calcific aortic stenosis (table 1). However, much of the evidence is conflicting and limited by the retrospective nature of the studies. The most consistent and strongest predictors of disease progression are severity of stenosis at baseline and degree of valvar calcification: the more severe the stenosis and the more heavily calcified the valve, the faster the rate of progression.[12 13] Clinical outcome is also influenced by the degree of valvar calcification, with nearly 80% of patients with moderate to severe calcification progressing rapidly (> 0.3 m/s/year) either to death or to aortic valve replacement within two years.[13]

Table 1 Risk factors for calcific aortic stenosis

Clinical
Age
Male sex
Smoking
Hypertension
Diabetes mellitus
Coronary artery disease
Chronic renal failure
Paget's disease
Hyperparathyroidism
Biochemical
Hyperlipidaemia*
Hypercalcaemia
Raised serum creatinine

*Low density lipoprotein, Lp(a) lipoprotein.

NOVEL TREATMENTS FOR CALCIFIC AORTIC STENOSIS

Current management of patients with aortic stenosis comprises monitoring disease progression and ensuring patient awareness of the need for antibiotic prophylaxis against the relatively low risk of infective endocarditis. For those patients with severe symptomatic disease, aortic valve replacement is a priority with conventional medical treatment reserved for symptom control in inoperable cases. However, the majority of patients with aortic stenosis do not have symptoms or an indication for surgery. Are there any interventions that can halt or slow the progression of the disease process? Theoretically, anti-inflammatory and antiproliferative agents would be anticipated to alter the natural history of aortic stenosis. Statins and angiotensin converting enzyme (ACE) inhibitors are two commonly used treatments that have proven secondary preventative benefits in cardiovascular disease and exhibit some of these desirable anti-inflammatory and antiproliferative properties.

Statins

Hydroxymethylglutaryl coenzyme A reductase inhibitors, or statins, are now well established in the primary and secondary prevention of coronary artery disease. Several studies have suggested that these drugs can cause regression of coronary artery disease and reduce the calcific volume of coronary plaques.[14] Given the clinical association of calcific aortic stenosis with hyperlipidaemia and coronary artery disease, and the striking histological similarities with atheroma, the hypothesis that statins may have the potential to influence disease progression in aortic stenosis is intriguing.[15]

Recent retrospective studies have suggested that statins may delay disease progression in aortic stenosis (table 2[16–22]) through their lipid lowering and anti-inflammatory actions.[16–19] These observational data should be interpreted with caution, since none of these studies were prospective randomised trials, serum LDL cholesterol concentrations did not correlate with disease progression, and the statin doses were small. There also appears to be some publication bias with studies reporting negative findings underrepresented in the literature.[20 21]

Table 2 Summary of trials assessing progression of aortic stenosis by repeated echocardiography

	Study and reference						
	Aronow *et al*[16]	Novaro *et al*[17]	Bellamy *et al*[18]	Rosenhek *et al*[19]	Samal *et al*[20]	Antonini-Canterin *et al*[21]	Cowell *et al*[22]
Design	RO	RO	RO	RO	RO	RO	Prospective RCT
Patients	180	174	156	211	112	242	134
Patients taking statin	62	57	38	50	55	121	65
Mean age (years)	82	68	77	70	73	68	68
Mean follow up (months)	33	21	44	24	NA	54	25
Total cholesterol (mmol/l)	NA	5.5	5.8	5.8	NA	NA	5.7
Correlation of progression with LDL cholesterol	NA	Yes/no	No	No	Yes	NA	No
Reduced progression with statin	Yes	Yes	Yes	Yes	No	No	No

LDL, low density lipoprotein; NA, not available; RCT, randomised controlled trial; RO, retrospective observational study.

Results of the SALTIRE (Scottish aortic stenosis and lipid lowering therapy, impact on regression) trial were recently reported. It was the first double blind randomised controlled trial of lipid lowering treatment in patients with calcific aortic stenosis.[22] This trial of 155 patients showed that, although atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations, it did not halt the progression or induce regression of the valve disease process as measured by Doppler echocardiography or helical computed tomography (fig 3). This occurred despite the association of atorvastatin with major reductions in serum C reactive protein concentrations (unpublished observations).

Given the data linking aortic stenosis with atherosclerosis and hypercholesterolaemia, why did intensive lipid lowering treatment not halt the progression of calcific aortic stenosis? One potential explanation is that, while these features may drive the initiation of aortic stenosis, disease progression may depend on other factors. The aortic valve is subjected to continuous dynamic mechanical stress, and leaflet plasticity and structure can have an overriding influence, such as with a bicuspid valve. Moreover, in contrast to atherosclerosis, aortic stenosis is associated with a virtual absence of smooth muscle cell proliferation and lipid laden macrophages, and is dominated by earlier and more extensive mineralisation. Decreasing the lipid pool and increasing the fibrous cap may be less relevant to the progression of aortic stenosis than it is for the reduction of atherosclerotic plaque rupture with statins in patients with coronary heart disease.

It may be argued that lipid lowering treatment is unlikely to influence disease progression in the presence of significant aortic stenosis. Patients with aortic velocities below 2.5 m/s were excluded from the SALTIRE trial, and intervening at this earlier stage of the disease process may have been more beneficial. However, such patients do not commonly present to routine clinical practice and their identification would potentially require population screening. Moreover, the SALTIRE trial was unable to exclude a modest treatment benefit (a delay in disease progression of < 0.07 m/s/year or $< 5\%$ aortic valve calcification/year). Although such modest reductions are unlikely to be meaningful in the majority of older patients, a small decrease in disease progression may be clinically important in younger patients with mild disease who may progress over many years. Indeed, a small preliminary observational study suggests that statins may reduce disease progression in patients with aortic sclerosis.[21]

Statin treatment of patients with aortic stenosis may confer secondary preventative benefits that are independent of its effects on the valve disease process because of the association between aortic stenosis and coronary artery disease. The SALTIRE trial was not powered to assess the benefits of lipid lowering treatment on cardiovascular end points, such as non-fatal and fatal myocardial infarction, but there was a trend in favour of reduced clinical events. Aortic stenosis and sclerosis may be important markers of occult vascular disease and thereby identify patients who would gain from the preventative benefits of statins. Larger clinical end point trials, such as the SEAS (simvastatin and ezetimibe in aortic stenosis) and ASTRONOMER (aortic stenosis progression observation: measuring effect of rosuvastatin) trials, will be able to address this issue.

Lastly, for many patients with aortic stenosis, the first symptom to develop is chest pain, and this precipitates the decision to replace the aortic valve. However, this may be driven by concomitant coronary artery disease rather than progression of valvar stenosis. Previous secondary prevention trials in coronary heart disease have reported a reduction in coronary artery bypass graft surgery rates.[23] Thus, the larger clinical end point trials of statins in aortic stenosis may suggest a reduction in the rate of valve surgery, but this may be driven by patients with aortic stenosis who undergo combined aortic valve and bypass surgery for symptoms of angina pectoris. If statins truly reduce disease progression then a reduction in isolated aortic valve replacement would be anticipated.

ACE inhibition

There are several reasons to believe that ACE inhibitors may have a role in the management of patients with aortic stenosis. Firstly, in contrast to normal valves, sclerotic aortic valve tissues demonstrably express angiotensin II and ACE, which may contribute to valve inflammation, calcification, and disease progression.[24 25] Secondly, the pressure overload induced by aortic stenosis has several effects on the myocardium including left ventricular hypertrophy, apoptosis, and fibrosis. This may accelerate the left ventricular systolic and diastolic dysfunction associated with aortic stenosis. Lastly, blood pressure lowering indirectly reduces the pressure overload of the left ventricle and potentially reduces the mechanical stress and strain on the aortic valve.

Two preliminary observational studies with ACE inhibitors have produced conflicting results. In a retrospective analysis of 211 patients, Rosenhek *et al*[19] found that progression of aortic stenosis was not delayed in patients maintained on ACE inhibitors. Furthermore, the presence of hypertension did not appear to influence the outcome. In contrast, O'Brien *et al*[24] found that ACE inhibitor treatment was associated with a 71% reduction in the progression of aortic valve calcification in 123 patients with aortic stenosis undergoing electron beam computed tomography. However, such retrospective observational data are difficult to interpret and the study findings have wide confidence intervals.

Historically, ACE inhibition was said to be contraindicated in patients with aortic stenosis. This has primarily been due to the concern of invoking profound peripheral vasodilatation that would result in haemodynamic compromise, collapse, and potentially death. However, patients with aortic stenosis

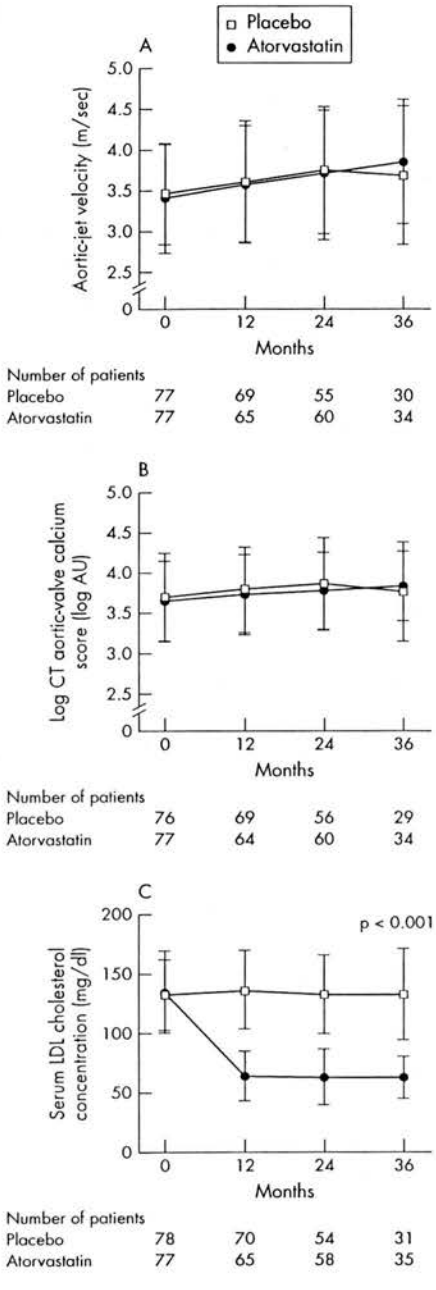

Figure 3 Effect of atorvastatin (80 mg daily) on the progression of aortic stenosis and serum low density lipoprotein (LDL) concentrations.[22] AU, arbitrary units; CT, computed tomography.

tolerate ACE inhibitors very well on initiation[26 27] and many patients (about 30%) with aortic stenosis are unknowingly established on such treatment without compromise. Indeed, the use of ACE inhibitors appears to confer long term survival benefit on patients considered to have a contraindication including those with aortic stenosis.[28] The potential beneficial haemodynamic and cardiac effects of ACE inhibition are increasingly being recognised and warrant further study in patients with aortic stenosis.[29]

CONCLUSIONS

The need for an alternative to aortic valve surgery is highlighted by the increasing longevity of the population and rising prevalence of aortic stenosis. New therapeutic strategies to limit disease progression are needed to delay, and potentially avoid, the need for valve surgery.

Statins and ACE inhibitors are two potential and promising treatments that may have beneficial effects in patients with aortic stenosis. Statins are likely to reduce cardiovascular events rather than disease progression per se but may potentially be a valuable preventative treatment in these patients. However, we must await the results of ongoing large randomised controlled trials to define the role of statins.

The prejudice against the use of ACE inhibitors by patients with aortic stenosis is changing.[23–26] We would argue that there is sufficient theoretical evidence to support the conduct of a randomised controlled trial to explore further its potential benefits. In the meantime, the cautious use of ACE inhibition by patients with concomitant hypertension, coronary heart disease, or heart failure seems appropriate.

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IMAGES IN CARDIOLOGY

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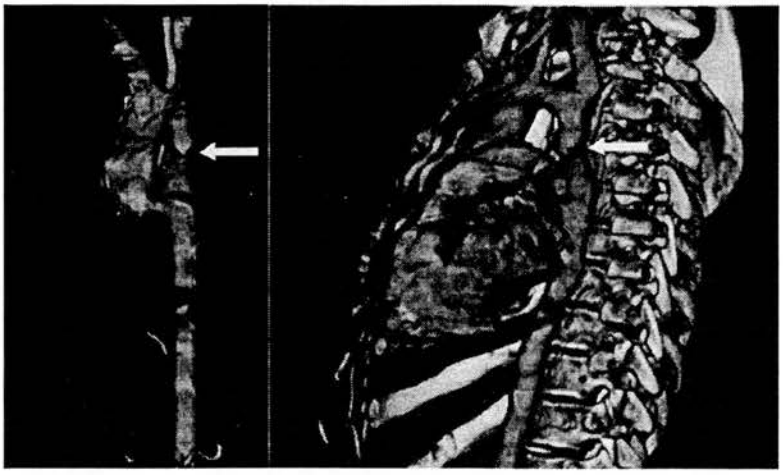
A common cause of secondary hypertension: coarctation of the aorta

A 16 year old male was referred to our department with hypertension refractory to medical treatment. He had recurrent episodes of headache. On physical examination, his blood pressures in right and left arms were 190/120 and 180/120 mm Hg, respectively. Also a systolic ejection murmur of grade 2/6 was present at the left upper sternal border radiating to the interscapular region. Femoral pulsations were diminished. The ECG revealed left ventricular hypertrophy. The chest *x* ray showed no pathology, but echocardiography revealed a bicuspid aortic valve, left ventricular hypertrophy, normal ascending aortic size, and an ejection fraction of 67% with normal systolic and diastolic dimensions. By using continuous wave Doppler, a 50 mm Hg pressure gradient was assessed 3–4 cm from the left subclavian artery with the suprasternal notch view. Computed tomographic angiography (CTA) of the thoracic aorta was performed. CTA showed a significant coarctation of the thoracic aorta distal to the origin of the left subclavian artery (panel). It was decided to undertake surgical intervention to correct the problem.



Computed tomographic angiography of the thoracic aorta showing a significant coarctation beyond the origin of the left subclavian artery (arrows).

Hypertension in teenagers and young adults is uncommon. As secondary causes are more commonly found in this age group than in older adults, aortic coarctation should be considered. Thus, palpation of femoral pulses and measurement of blood pressure in the limbs should be performed in every hypertensive young patient. Early diagnosis and treatment are essential for the prevention of morbidity and mortality from premature cardiovascular complications. Surgical or percutaneous techniques should be performed together with medical treatment to prevent end organ damage.

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